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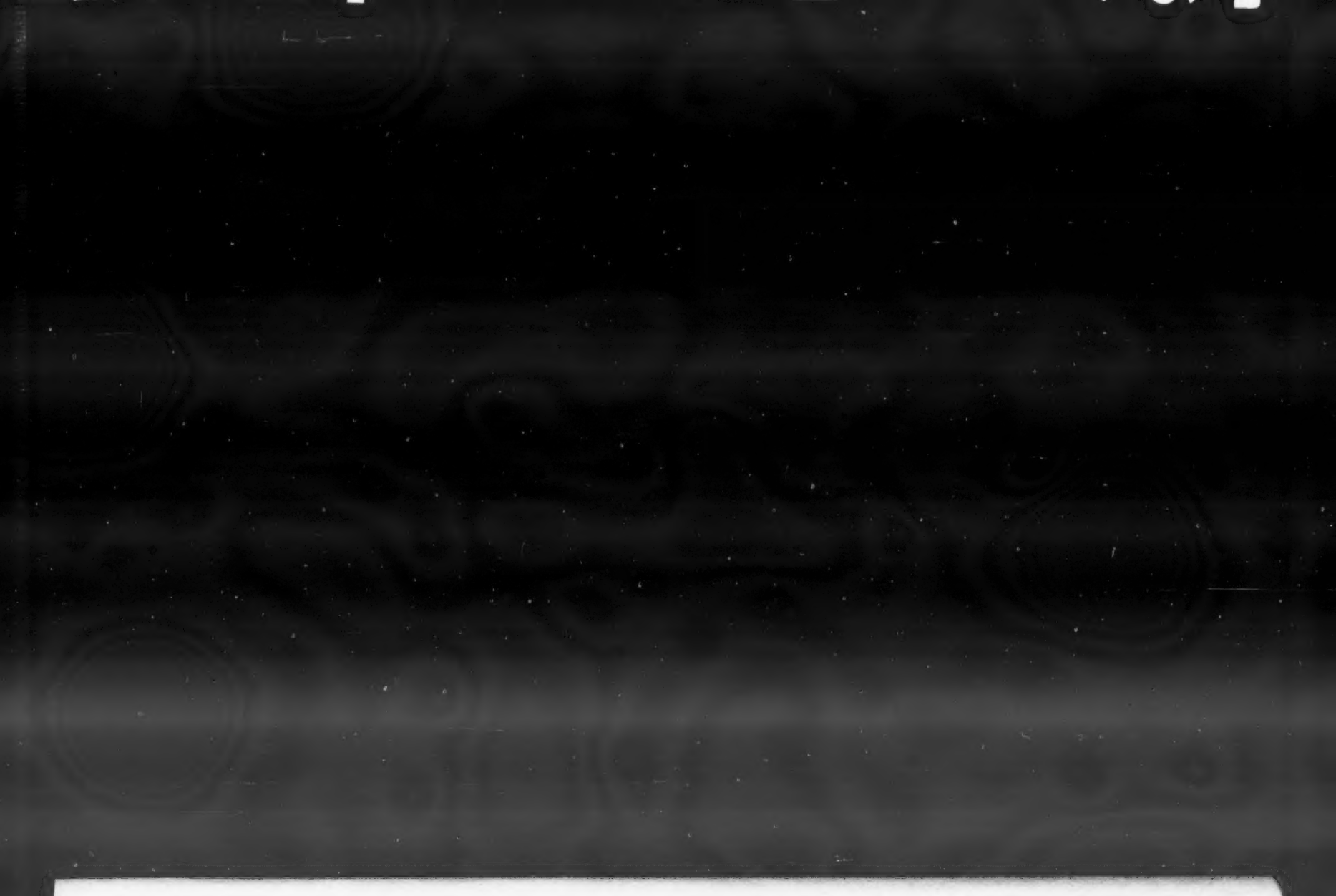

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HYSTERICAL LARYNGEAL SPASM AND THE PRODUCTION OF PAROXYSMAL ARTERIAL HYPERTENSION[1]

By J. H. TYRER, B. T. EMMERSON, and K. J. MURPHY

(From the Medical Professorial Unit (University of Queensland), Brisbane Hospital, Brisbane, Australia)

With Plates 21 to 23

'. . . The organ of generation becoming rebellious and masterful, like an animal disobedient to reason, . . . closes up the passages of the breath, and, by obstructing respiration, drives them to extremity, causing all varieties of disease.'—Plato, *Timaeus*.

Hysterical laryngeal spasm is not common, and according to Jackson (1949) psychosomatic laryngeal disturbances are almost always phonatory or tussive. But the condition has long been recognized (Nothnagel, 1881). Hajek (1932) and Wessely (1944) described it, but also gave separate descriptions of purely inspiratory hysterical laryngeal spasm ('der inspiratorische, funktionelle Stimmritzenkrampf'), in which expiration was unimpeded. Jackson and Jackson (1937) described hysterical laryngeal spasm, giving theoretical reasons why such spasm is chiefly inspiratory. Other descriptions of hysterical inspiratory laryngeal spasm were given by Morrison (1939) and Thomson, Negus, and Bateman (1955). Suggit and Hilton (1953) mentioned that laryngeal spasm may be functional, Ballenger and Ballenger (1957) that it may occur in neurosis. In the above references no description can be found of purely expiratory laryngeal spasm in hysteria. Allen (1947) reported a case of conversion hysteria with expiratory stridor, but 'no structural interference with the airway was demonstrated in the nasal passages or in the larynx'. De Greeff, Boxus, and André (1949) described a patient with hysterical dyspnoea who, especially during expiration, emitted a low-pitched sound audible quite a distance away. This sound resembled neither true laryngeal obstruction nor asthmatic wheezing, but was possibly of tracheal origin. It was designated *pseudo-spasme laryngé*, for a bronchoscope readily passed through the larynx without obstruction.

Two hysterical patients are described below. The first had attacks of purely expiratory laryngeal spasm, inspiration being unobstructed. The second had attacks of inspiratory laryngeal spasm initially, expiratory spasm later becoming added and dominant. Both patients could speak during this hysterical expiratory laryngeal spasm, which is a condition quite distinct from phonic spasm ('aphonia

[1] Received July 11, 1958.

spastica'). Phonic spasm is an intention spasm in excessive voice users, occurring only on attempted phonation, and is related to occupational neuroses such as 'writer's cramp' (Hajek, 1932; Morrison, 1939; Wessely, 1944; Suggit and Hilton, 1953; Thomson, Negus, and Bateman, 1955; Ballenger and Ballenger, 1957). Jackson and Jackson (1945), however, regarded phonic spasm as an occupational disability due to the local trauma of excessive use of the voice rather than to neurosis. Nothnagel (1881) preferred the term 'incoordination spasm of the vocal cords' to 'aphonia spastica'. He described a patient in whom other voluntary movements besides phonation precipitated laryngeal spasm—for example, attempting to blow out the flame of a candle. This patient in addition sometimes had hysterical inspiratory laryngeal spasm, causing dyspnoea.

Case Reports

Patient No. 1. In June 1957 a 59-year-old woman was referred to the Brisbane Hospital for the investigation of incapacitating attacks of headache and precordial pain, during which it had been noted that her arterial blood-pressure rose to severely hypertensive levels. The episodes had occurred for about 18 years, and it was suggested that the patient might have a phaeochromocytoma.

After her admission to hospital attacks lasting 15 to 30 minutes occurred almost daily, though at no special time, and sometimes two or three times daily. This had been the frequency pattern of attacks for several months; for the previous 18 years the incidence had at times been similar, but sometimes several weeks elapsed between attacks. The patient stated that each episode began with a feeling of tightness in the chest and throat, followed within a minute by headache and an intense feeling of pressure inside the skull; her face felt hot and flushed, and the blood seemed to rush to her head. The sense of tightness would then increase to actual pain in the chest and neck, usually causing her to groan because of its severity; breathlessness and palpitations would by this time add to her discomfort. On examination during such attacks the patient seemed very distressed, frequently groaning and clutching her chest and complaining of headache and chest pain. The skin of the face, throat, and upper chest was flushed, warm, and dry. The cervical veins were engorged, the jugular venous pressure rising to 4 to 6 cm. above the medial end of the clavicle (trunk inclined 45 degrees to the horizontal). The respirations were slow, varying from seven to 12 per minute; the radial pulse was rapid, usually 130 to 150 per minute. Several independent observers recorded arterial hypertension to levels of 220 to 280 systolic and 110 to 170 diastolic in different attacks. Typical respiratory and pulse rates and blood-pressure readings between attacks were 14 to 18 per minute, 70 to 80 per minute, and 130/80 respectively. No tremors, pupillary dilatation, or glycosuria were associated with the attacks.

It was found that an intravenous injection of 10 mg. of phentolamine in 5 ml. of normal saline would terminate an attack within one or two minutes, with restoration of arterial blood-pressure to normal. As a provocative measure 0·05 mg. of histamine base in the form of histamine acid phosphate was injected intravenously, a syringe containing phentolamine being held in readiness. This was followed within a few minutes by a typical attack and a rise of arterial blood-pressure from 135/80 to 230/130. It was also found that intravenous injections of 0·5 to 1·0 ml. of normal saline could both provoke and terminate attacks when the patient thought that histamine and phentolamine respectively

were being used (Plates 22 and 23, Fig. 5*a*, *b*, *c*, *d*). This result appeared to indicate that psychogenic mechanisms could initiate and abolish the episodes. Assay of catechol amines in a 24-hour urine specimen, an attack having occurred within this time, yielded normal values on two occasions.

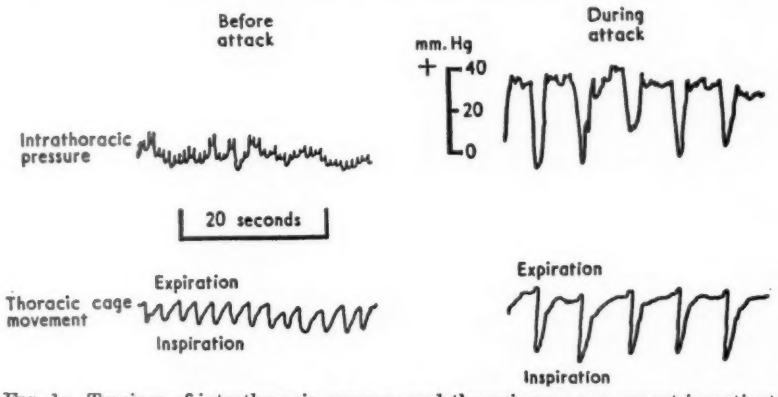

FIG. 1*a*. Tracings of intrathoracic pressure and thoracic cage movement in patient No. 1 before and during attack (induced by an intravenous saline injection). Before the attack the arterial pressure was approximately 140/90. For the period of tracings shown in the attack the arterial pressure during expiration was between 180/125 and 190/130. The systolic pressure during the short inspirations was 110 to 130 (see p. 318).

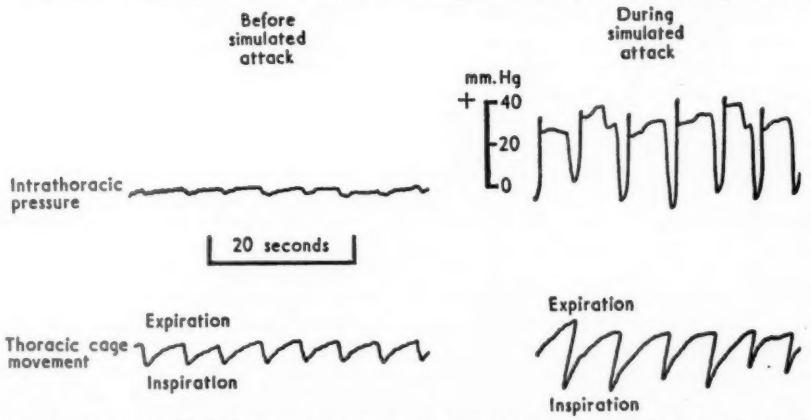

FIG. 1*b*. Tracings of intrathoracic pressure and thoracic cage movement in a control subject (J. H. T.), simulating the abnormal respiratory dynamics in patient No. 1. The resting arterial pressure was approximately 135/90. During the simulated attack the tracings are comparable to those obtained from the patient during her attack. For the period of tracings shown the arterial pressure during expiration was between 170/115 and 190/135. The systolic pressure during the short inspirations was 120 to 135 mm. Hg (see p. 321).

When it was found that attacks were readily produced by suggestion and saline injected intravenously, the changes in arterial blood-pressure could be studied more closely. During attacks the blood-pressure rose comparably in the arteries of all four limbs. Further, if for example the blood-pressure had risen to 250/140 in a particular attack, and the sphygmomanometer cuff was kept inflated at 250 mm. Hg, the Korotkov sounds (Korotkov, 1905) were

audible only during expiration, which was prolonged, there being auscultatory silence during inspiration, which was of short duration; by gradually lowering the pressure in the sphygmomanometer cuff the pressure at which auscultatory sounds appeared during inspiration was noted, and thus the systolic pressures during expiration and inspiration could be compared. Analogously, the diastolic pressures during expiration and inspiration could be compared; but the diastolic pressure during inspiration was often difficult to determine. Typical arterial blood-pressure readings during an attack of moderate severity were 250/140 during expiration and 130/90 during inspiration. Such sphygmomanometric measurements were facilitated because, during attacks, respirations were slow (seven to 12 per minute), while the heart rate was fast (130 to 150 per minute), so that an adequate number of Korotkov sounds could be heard during each respiratory cycle. During an attack expiration was much longer in duration than inspiration (see Fig. 1*a*), and hence the inspiratory remissions of the arterial hypertension at first easily escaped notice on routine sphygmomanometry.

The remissions of the expiratory arterial hypertension during inspiration suggested that the patient might be forcibly expiring against a partly closed glottis. Indeed, the general appearance of distress, combined with semi-articulate and articulate groans such as 'Oh, the pain!', had at first concealed expiratory straining and an expiratory laryngeal stridor. The expiratory stridor, clearly heard on auscultation over the larynx, suggested adductor spasm of the vocal cords during expiration. No stridor could be heard during inspiration. The flushed face and neck, and engorged cervical veins, were consistent with expiratory straining against vocal cords in adductor spasm, producing manœuvres of the Valsalva type (Valsalva, 1707), repeated with every respiratory cycle during an attack. Laryngoscopic examination confirmed intense adductor spasm of the vocal cords during prolonged expirations, the expired air being slowly forced out between the tightly adducted cords. There was wide abduction of the cords during the intervening short inspirations. On one occasion a thin-walled rubber balloon (capacity approximately 50 ml.) was passed into the oesophagus and connected by a water-filled polythene tube of 3 mm. bore to a recording mercury manometer, so that intrathoracic pressures, as reflected by intra-oesophageal pressures, could be recorded before and during an induced attack. On this occasion the induced attack was less severe than usual, probably because the patient was made uncomfortable by the swallowed tube and balloon. Intrathoracic pressures during expiration, however, rose by 35 to 40 mm. Hg. A simultaneous record of thoracic cage movement also showed the prolonged expirations and short abrupt inspirations (Fig. 1*a*). The expiratory arterial pressure during this attack rose from 140/90 to 180–220/120–130. The systolic pressure during the short inspirations was 110 to 130. When the patient knew an attack was to be induced, there was frequently an initial psychogenic tachypnoea of 24 to 28 respirations per minute; this did not affect the resting arterial pressure readings.

The patient had a long, psychiatrically significant history, with a disastrous early marriage followed by insoluble problems and fears regarding her four subsequent children, the oldest of whom was 37 in 1957. The attacks were more numerous and severe when the patient was emotionally disturbed or thwarted, and the more severe attacks gathered her sons and daughters closer to her. There had been gynaecological operations: for prolapsed uterus in 1924, removal of an ovary in 1927, and tying of the Fallopian tubes in 1937; bilateral simple mastectomy was performed in 1946, apparently for hyperplastic cystic disease. After psychotherapy, including hypnotic suggestion and explanation of

the mechanism of her symptoms, and adminstration of capsules of lactose as a psychological support against severe attacks, the patient was discharged. She was seen 11 months later. She then said the attacks had been milder and far less frequent, with periods of two or three weeks between attacks, while she asserted that great help was obtained from the capsules in preventing any severe attacks.

Hysterical expiratory adductor spasm of the vocal cords leading to forced obstructed expirations, with consequent haemodynamic disturbance, thus seemed responsible for the clinical features of the attacks, including the paroxysmal arterial hypertension.

Patient No. 2. A man of 61 years, of no fixed employment, was referred to the Brisbane Hospital in August 1957. From 1949 to 1957 he had suffered at least 30 attacks of very severe breathlessness, the duration of which varied from about one hour to a few days. More than half of these attacks had been complicated by apparent unconsciousness, which in turn was occasionally associated with 'fits'. He had been admitted to hospital apparently unconscious on four occasions; on several other occasions, after admission to hospital because of breathlessness, episodes of apparent unconsciousness ensued. The patient's wife had suffered from asthma, and his first attack of breathlessness occurred at her funeral in 1949: he then experienced a sense of suffocation and tightness in the throat and chest, followed by apparent unconsciousness for several hours.

Some observers had regarded the subsequent dyspnoeic attacks as asthmatic in type, others had been impressed by laryngeal spasm producing high-pitched stridor over the larynx, either during inspiration only or during both inspiration and expiration. This stridor obscured the breath sounds on auscultation of the chest. In general the attacks had been little relieved by the usual sympathomimetic drugs used in asthma, or by aminophylline, better responses being obtained by sedation. When the respiratory distress was followed by unconsciousness, it had been noted on some occasions that the patient's colour was normal, on others that cyanosis was present. On one occasion, when the patient was cyanotic, sulphaemoglobinaemia was demonstrated; the patient had been taking tablets of aspirin, phenacetin, and caffeine for headaches during the attacks. Once, in 1952, respiratory distress and an appearance of impending suffocation led to intubation of the larynx with a Magill's tube; at this time marked adductor spasm of the vocal cords during inspiration was seen laryngoscopically, though the cords were abducted widely during expiration. Passage of the Magill's tube promptly relieved the respiratory distress.

While the patient was under observation in August 1957 numerous attacks of laryngeal spasm occurred, either spontaneously or induced by suggestion combined with 1 ml. of normal saline subcutaneously injected. These attacks began with inspiratory laryngeal spasm, which produced high-pitched inspiratory stridor audible over the larynx and also several feet away, obscuring the breath sounds on auscultation of the chest. The patient then complained of breathlessness, a feeling of suffocation, and tightness in the chest and throat. The obstruction to inspiration was reflected by a marked use of accessory respiratory muscles and a hollowing of the neck above the clavicles during inspiration (Plate 21, Fig. 4*a*, *b*). At this stage there appeared to be no significant alteration of the patient's arterial blood-pressure from its usual resting value of 140/90. After about 10 minutes of purely inspiratory laryngeal spasm, expiratory laryngeal spasm frequently occurred in addition, and tended to dominate the clinical picture. This caused congestion of the face and engorgement of the cervical veins during prolonged expirations, and the patient added headache to

his complaints. Inspiration by this time was shortened. The high-pitched inspiratory and expiratory laryngeal sounds, audible several feet from the patient, were very loud on auscultation over the larynx. At the same time closely similar sounds could be heard on auscultation over the lung fields, resembling the sounds heard in ordinary bronchial asthma. During one such episode, induced by suggestion, the patient's vocal cords were observed laryngoscopically to be in intense adductor spasm during both shortened inspiration and prolonged expiration; under local anaesthesia a No. 8 Magill's tube was inserted between the vocal cords, and this abolished the high-pitched inspiratory and expiratory sounds audible over the larynx. High-pitched continuous adventitious sounds, however, could still be clearly heard over the lung fields during both inspiration and expiration, indicating that there was constriction of the trachea or the bronchial tree, or both, in addition to laryngeal spasm.

During the phase of expiratory laryngeal spasm it was observed that the patient's systemic arterial blood-pressure rose from values of approximately 140/90 to values during expiration of 200–240/110–150, with remission during inspiration. Measurements of intrathoracic pressure (as in patient No. 1) during this phase indicated that positive pressures of 40 to 60 mm. Hg were achieved during expiration. On several of his previous admissions to hospital arterial hypertension had been recorded during respiratory distress.

One attack of laryngeal spasm induced by suggestion was complicated by apparent unconsciousness, which in turn was followed by a fit of clearly hysterical type: shaking of all four limbs, side-to-side head rolling, barking noises, and churning of saliva with the tongue; during this time there was no cyanosis, the corneal reflexes were present, and the plantar responses were flexor. Some of the previous episodes of apparent unconsciousness also appeared to have been complicated by hysterical fits. On the other hand, some of the fits complicating the laryngeal spasm may have been epileptic in nature and facilitated by anoxia: in these the patient had been reported to be cyanotic, the tongue had been bitten, and urine had been passed; a recent electroencephalogram revealed a generalized cerebral dysrhythmia consistent with idiopathic epilepsy. Certain other symptoms during laryngeal spasm were likewise consistent with anoxia as well as with hysteria: mental confusion, drowsiness, restlessness, inability to speak coherently, and degrees of clouding of consciousness varying up to apparent unconsciousness with lack of response to painful stimuli.

The patient had exhibited hysterical evasion from responsibilities for more than 40 years. He had been discharged from the Australian Army after a minor injury to his jaw in France (January 1917). He had sought without success an Australian Repatriation Pension on numerous grounds, for example 'shell shock', neurasthenia, and 'stomach disease', but was finally granted an Invalid Pension. Laryngeal spasm, with impressive dyspnoea and occasional attacks of apparent unconsciousness, was a useful addition to his repertoire, which included a left hemiparesis and left hemianaesthesia, with fluctuations in severity and other contradictory features. Psychotherapy was attempted before the investigatory studies, but was unsuccessful. In this hysterical patient analysis of the mechanism of abdominal pseudo-distension has also been described (Tyrer, Murphy, and Emmerson, 1958).

Control Studies

The three authors practised simulation of the abnormal respiratory dynamics of patient No. 1. A positive intrathoracic pressure of 35 to 60 mm. Hg was maintained by forced obstructed expirations for about three-quarters or more of

every respiratory cycle for 15 to 30 minutes. The positive pressure was released during every intervening short inspiration, and the respiratory rate was kept at seven to 12 cycles per minute. The positive intrathoracic pressure was sometimes maintained by forcing expired air out between tightly adducted vocal cords; in these instances the intrathoracic pressure was recorded in the oesophagus from a balloon connected to a recording mercury manometer, as in patient No. 1. Alternatively the intra-oral pressure was recorded through a flanged mouthpiece connected to a Y-tube, one limb of which led to a recording mercury manometer, the other to a short rubber tube which could be constricted by a

Effects of Forced Obstructed Expirations on Intrathoracic and Arterial Pressures in Control Subjects

Blood-pressure measured by a mercury sphygmomanometer to the nearest 5 mm. Hg. Expiratory pressures measured in mm. Hg from the tracings of a recording mercury manometer.

Subject and experiment	*Initial control period Resting blood pressure*	*Period of forced obstructed expirations*			
		Expiratory pressure (average of 10 successive respiratory cycles)		*Blood-pressure (average of three readings)*	
		Intra-oesophageal	*Intra-oral*	*Expiration*	*Inspiration (Systolic readings only)*
B. T. E. 1	140/90	42	..	190/130	135
2	120/80	..	38	180/125	130
3	120/80	..	55	220/130	120
K. J. M. 1	115/70	..	36	170/115	110
2	120/75	..	38	200/125	130
J. H. T. 1	135/90	41	..	200/140	135
2	125/80	..	39	180/120	140
3	135/85	..	58	240/145	135

clip to obstruct expiration. Considerable practice was required before pressure tracings could be obtained to simulate those obtained from patient No. 1 during a hysterical attack. Each of the three authors could induce in himself severe arterial hypertension during the forced obstructed expirations, with remission of the hypertension during every intervening short, unobstructed inspiration (see Table). The sphygmomanometric technique was as described in the investigation of patient No. 1. In one control subject the sphygmomanometric findings during the forced obstructed expirations were confirmed by direct recording of intra-arterial pressure through a B.D. Cournand needle in the left brachial artery. This was connected to a Statham physiological pressure transducer. A Statham transducer was also used to record simultaneously the intra-oral pressure. All tracings were recorded photographically by means of an amplifying system (Electronics for Medicine, Inc.) (Figs. 2 and 3). Most of the other clinical features of the hysterical attacks of patient No. 1 could also be readily reproduced: flushing of the face, neck, and upper chest, cervical venous engorgement; a feeling of fullness in the head amounting to considerable discomfort; palpitations; and, after five to 10 minutes of an 'attack', a sense of tightness and muscular fatigue in the chest and throat.

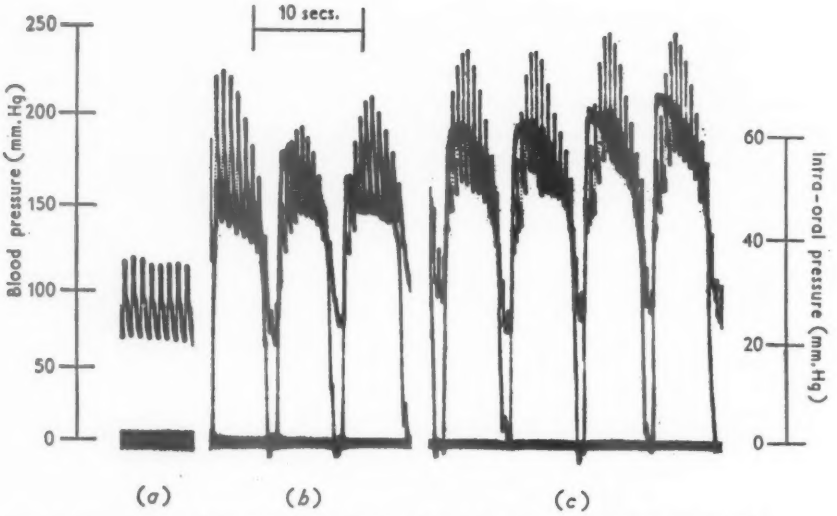

FIG. 2. Simulation of the attacks in Patient No. 1 by a control subject (J. H. T.).

(*a*) Brachial artery pressure tracing during control rest period (approximately 120/70). (*b*) and (*c*) Brachial artery pressure, and simultaneous intra-oral pressure tracings. (*b*) Arterial hypertension occurred during each prolonged forced obstructed expiration, and remitted during each short unobstructed inspiration. The return of the intra-oral pressure tracing to the base line marks inspiration as distinct from expiration. (*c*) With intra-oral pressures during expiration slightly higher (between 60 and 70 mm. Hg), arterial pressure during expiration rose to approximately 250/175, again with remission of the hypertension during the short inspirations.

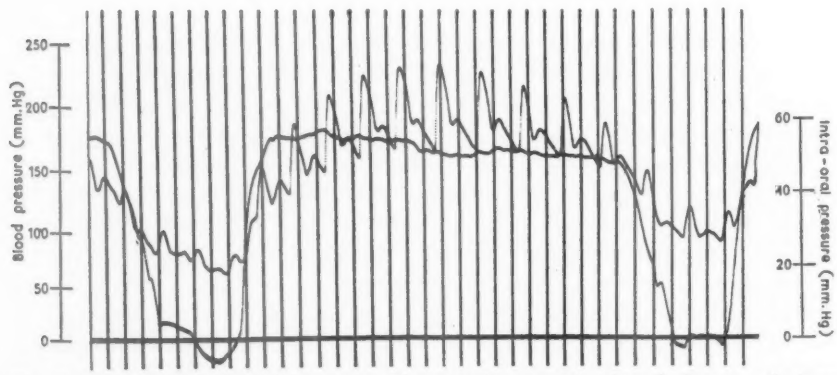

FIG. 3. Analysis of the brachial artery and intra-oral pressure tracings during a respiratory cycle such as in Fig. 2(*b*). During the forced obstructed expiration with the intra-oral pressure maintained between 50 and 60 mm. Hg, the arterial pressure rose to approximately 235/165. During the subsequent unobstructed short inspiration the arterial hypertension remitted.

The return of the intra-oral pressure tracing to the base line marks inspiration as distinct from expiration. The time marker indicates 0·2 seconds.

Discussion

Patient No. 1. The paroxysms of headache, chest pain, palpitations, and arterial hypertension led to reference of the patient for possible phaeochromocytoma. Atypical features, which did not exclude the condition, were: (1) a normal arterial blood-pressure between attacks after an 18-year history; Hamilton, Litchfield, Peart, and Sowry (1953) reported a case having normal 'interval' blood-pressure with a definite eight-year (and possibly 20-year) history of paroxysms before removal of the phaeochromocytoma; (2) the flushed, warm, and dry skin of the face, neck, and upper chest. Usually the skin is pale, cold, and sweating during the paroxysms (Pickering, 1955). Maddox (1957), however, described attacks with generalized flushing, though with profuse sweating, in a patient whose phaeochromocytoma was removed at operation. The provocative histamine test (Evans, Rubitsky, Bartels, and Bartels, 1951) and the lowering of hypertension by the adrenolytic drug phentolamine (Helps, Robinson, and Ross, 1955) have been used in the diagnosis of phaeochromocytoma, though false positive results may occur. Our patient gave a positive response to both these tests, and so hysteria may be added to the list of causes of 'false positives'. In reassuring the patient in her distress, she had been told that the phentolamine would stop her attack, which it did. Again, the patient had been warned before the provocative histamine test that an attack was likely to be produced, and it was. After this initial conditioning, paroxysms could be provoked and terminated by intravenous injections of 0·5 to 1·0 ml. of normal saline, provided the patient thought histamine and phentolamine respectively were being used. The conditioning was specific for saline injected intravenously; subcutaneous injections would not produce attacks. At this stage it was clear that psychogenic factors could produce the attacks. Smirk (1957), however, noted that with phaeochromocytoma paroxysms of hypertension may occur as the result of emotion; and Raab (1953) cited hyperventilation as provoking hypertensive paroxysms in some cases of phaeochromocytoma, an effect possibly attributable to a mechanical, massaging action of the diaphragm. Psychogenic disturbance is an important cause of hyperventilation. On the other hand, (1) it was difficult to see how psychogenic factors could abruptly terminate a paroxysm due to phaeochromocytoma; (2) in our patient an assay of urinary catechol amines was normal on two occasions after paroxysms; Bishop (1956) regarded this test as extremely reliable; and (3) the pattern of expiratory arterial hypertension with remission during every inspiration could hardly be produced by a humoral mechanism. Thus phaeochromocytoma was excluded.

Pickering (1955) described attacks of anxiety with a rise of arterial blood-pressure in the differential diagnosis of the paroxysms of phaeochromocytoma, and Smirk (1957) also noted that anxiety states may cause confusion in diagnosis. Wolf and Wolff (1950) found that emotional stress could raise the arterial pressure of normal as well as hypertensive subjects, which is the experience of most physicians. Altschule and Shah (1952) observed that voluntary breath-holding

(for example, for 20 seconds) caused a rise of arterial pressure in normal, neurotic, and psychotic persons, which was associated with the retention of carbon dioxide in the blood. Certain apparently normal people can elevate their arterial pressure at will, apart from emotional or respiratory disturbance or increased physical activity (Whyte, 1958). The psychogenic hypertension in our patient is distinguished from these varieties of psychogenic hypertension by its occurrence during every expiration and remission during every inspiration.

Patient No. 2. The purely inspiratory laryngeal spasm at the onset of the hysterical attacks corresponded to the type of hysterical laryngeal spasm described by Hajek (1932) and others. When expiratory laryngeal spasm became added and dominant, arterial hypertension during the prolonged expirations occurred, as in the first patient, with remission during every shortened inspiration. It was of interest that during some previous sojourns in hospital the patient had been regarded as suffering from essential hypertension, though between attacks of laryngeal spasm he was clearly normotensive. In the attacks continuous high-pitched adventitious sounds were heard over the chest during the short inspirations and prolonged expirations, even when the laryngeal sounds were abolished by insertion of a No. 8 Magill's tube between the vocal cords. This appeared to indicate constriction of the trachea or bronchial tree, or both. The expiratory wheezing may have been produced by passive compression of the air passages by a raised intrathoracic pressure, as described by Dekker and Groen (1957). Such compression would not explain the inspiratory adventitious sounds, which were presumably due to active spasm of the trachea or bronchial tree. Our second case thus appears to be an example of tracheal or bronchial constriction, or both, in relation to a purely psychogenic stimulus. The literature dealing with psychogenic factors in asthma is voluminous. Dekker and Groen (1956) described psychogenic attacks of asthma reproducible under laboratory conditions.

Fluctuation of arterial and intrathoracic pressures. As is well known, arterial pressure is rhythmically elevated and lowered during ordinary quiet respiration; if inspiration and expiration become deeper, the variations of intrathoracic pressure increase, and the effects on arterial pressure are intensified (Wiggers, 1944). Fluctuations of arterial pressure in severe asthmatic attacks may be such that the systolic blood-pressure during expiration is 20 to 30 mm. Hg higher than during inspiration (Järvinen, 1957). The expiratory rises of intrathoracic pressure during the attacks of expiratory laryngeal spasm in both our patients were considerable (35 to 60 mm. Hg) even in only moderately severe attacks, and amounted to modified Valsalva manœuvres (Valsalva, 1707). These forced and prolonged obstructed expirations were repeated with every respiratory cycle for periods of 15 to 30 minutes, with corresponding gross fluctuations of arterial pressure. When the three control subjects voluntarily produced comparable fluctuations of intrathoracic pressure, they likewise had gross fluctuations of arterial pressure. The literature dealing with the Valsalva manœuvre has been reviewed by Liedholm (1939). More recent papers on the

subject include those of Rushmer (1947), Sarnoff, Hardenbergh, and Whittenberger (1948), Goldberg, Elisberg, and Katz (1952), Lee, Matthews, and Sharpey-Schafer (1954), Judson, Hatcher, and Wilkins (1955), and Sharpey-Schafer (1955). These authors agree that substantial rises of arterial pressure may occur during and after the Valsalva manœuvre and some of its modifications. Jones, Helrich, and Eckenhoff (1956) described modifications of the Valsalva manœuvre commonly seen during general anaesthesia. Associated with these (coughing, retching, forced expiration, positive-pressure airway ventilation) substantial rises of arterial pressure were encountered. Vaquez and Donzelot (1926) described a patient with an oesophageal carcinoma involving the larynx, and another patient with a mediastinal lymphosarcoma. Both these patients suffered dyspnoeic crises, with a rise of arterial pressure from 150 to 230 systolic in the first patient and from 170/80 to 270/110 in the second. The authors did not deem the degree of asphyxiation adequate to explain the rise of arterial pressure; in the first patient they considered the effects might be due to a reflex originating in the laryngeal plexus. No information was available regarding intrathoracic pressure changes during the dyspnoeic crises. The present paper describes two hysterical patients in whom forced obstructed expirations and the consequent expiratory rise of intrathoracic pressure adequately accounted for the pattern of paroxysmal arterial hypertension found clinically.

Reliability of the pressure measurements. Fry, Stead, Ebert, Lubin, and Wells (1952) concluded that changes in intra-oesophageal pressure quantitatively reflect changes in intrathoracic pressure when the oesophagus is relaxed. Wood (1956) stated that the intra-oral pressure 'may be assumed to be also the intra-bronchial and intrapleural pressure' when Valsalva manœuvres are performed by blowing up a column of mercury. As only relatively slow cyclic changes were being studied in our patients (seven to 12 cycles per minute), a recording mercury manometer was adequate for the purpose. Indeed Fig. 1*a* (before the attack) shows that the recording mercury manometer was sufficiently sensitive to record the heart rate at approximately 90 per minute after patient No. 1 had swallowed the rubber balloon connected to polythene tubing. As described in the record of this patient, the systolic levels of the fluctuating arterial pressure were readily compared sphygmomanometrically. Our findings agreed with those of Järvinen (1957) that the levels of diastolic pressure are often more difficult to compare, chiefly because of trouble in obtaining the diastolic reading during the short inspiration. Järvinen (1957) studied the fluctuations of arterial pressure in asthmatics and in normal subjects breathing through tubes of different calibre. He found the systolic readings obtained with a sphygmomanometer adequate when compared with direct intra-arterial pressure records obtained with a Sanborn electromanometer. Knowles, Gorlin, and Storey (1956), studying arterial pressure responses associated with the Valsalva manœuvre, found that sphygmomanometric readings correlated accurately with direct intra-arterial pressure tracings recorded simultaneously with a Sanborn electromanometer. Our experience was similar in one control subject.

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Summary

1. Hysterical laryngeal spasm is described in two patients. In the first patient the spasm was purely expiratory. In the second patient attacks began with inspiratory laryngeal spasm, but expiratory laryngeal spasm usually became added and dominant if the hysterical attack lasted longer than about 10 minutes.

2. Attention is drawn to an unusual type of paroxysmal arterial hypertension encountered in these patients. Forced obstructed expirations, in relation to hysterical expiratory adductor spasm of the vocal cords, caused severe arterial hypertension during the prolonged expirations; this arterial hypertension remitted during every short inspiration. The first patient had been referred for consideration of a possible phaeochromocytoma. The second patient had been regarded as having essential hypertension during a number of previous observations in hospital, but between attacks of laryngeal spasm he was clearly normotensive.

3. After practice, three apparently normal men could closely simulate the hysterical attacks as regards the pattern and severity of the arterial hypertension as well as other features.

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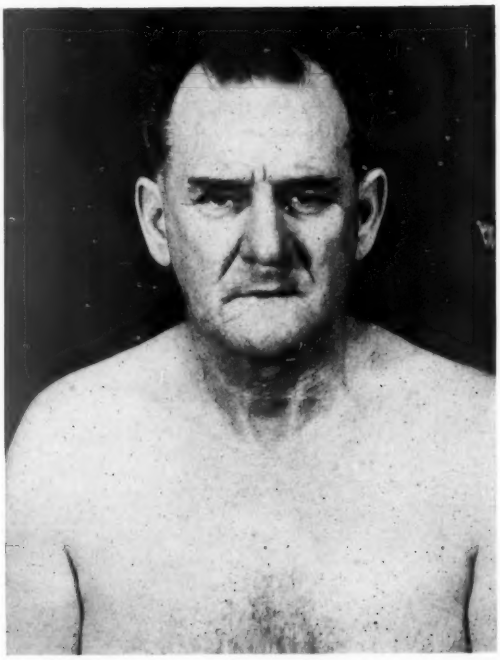

FIG. 4*a*. Patient No. 2 before an attack, during an ordinary inspiration

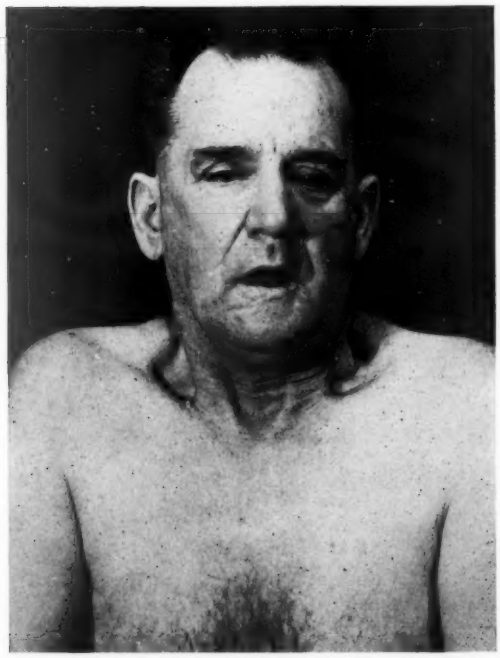

FIG. 4*b*. Patient No. 2 during an obstructed inspiration, in the stage of purely inspiratory laryngeal spasm. The sternomastoid muscles are prominent, the supraclavicular fossae hollowed, the shoulders held elevated, and the mouth open.

The attack was induced by suggestion and a subcutaneous saline injection approximately four minutes previously.

FIG. 5*a*. Patient No. 1 during the resting control period. Arterial pressure 130/85

FIG. 5*b*. Patient No. 1 two minutes after an intravenous injection of 0·5 ml. of normal saline. She said she was beginning to feel 'the rush of blood to the head' and the tightness in the chest and throat

FIG. 5c. Patient No. 1 at the height of an attack. Groaning about the severity of the headache and the chest pain, she clasps her chest. The facies is consistent with expiratory straining; the eyes are tightly closed.

Between Figs. 5*b* and 5*c*, the arterial pressure varied between 200/120 and 260/170 during the forced obstructed expirations. During the short unobstructed inspirations the systolic pressure varied between 120 and 140.

A second intravenous saline injection is being given, this time to terminate the attack.

FIG. 5*d*. Patient No. 1 within a minute of the second saline injection. The attack has ceased. The facies is characteristic, and the patient relaxes the clasping of her chest. The arterial pressure during the next 30 seconds was approximately 135/85 during both inspiration and expiration

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FOCAL GLOMERULONEPHRITIS[1]

A Study Based on Renal Biopsies

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With Plates 24 and 25

In the first half of the last century Richard Bright made his great contribution to medicine, recognizing that a proportion of patients who died with generalized oedema, or anasarca, were found at necropsy to have some disease of the kidneys, and that this disease might be recognized in life by finding in the urine heat-coagulable substances not dissolved by acid. He further found that there was a correlation between the presence of kidney disease and enlargement of the heart. Although describing different macroscopic appearances of kidneys, he made no published histological studies, nor did he attempt any classification of renal disease. The classical book on the histology of renal disease by Volhard and Fahr, published in 1914, was entitled *Die Brightsche Nierenkrankheit*, with three main divisions of renal disease: nephroses, nephritis, and arteriosclerotic kidney disease. Nephritis was divided into diffuse glomerulonephritis and focal (*herdformige*) nephritis; the latter was further subdivided into (*a*) focal glomerulonephritis; (*b*) interstitial nephritis; and (*c*) embolic focal nephritis.

With the difficulty of making an exact diagnosis of a renal lesion during life, the main interest in classification has centred around attempts to subdivide glomerulonephritis into clinical and pathological entities. The difficulties are emphasized by the still frequent use of the diagnostic label of Bright's disease attached to almost any patient with evidence of renal failure; although this evidence usually implies glomerulonephritis, it may also include pyelonephritis, arteriolosclerotic kidneys, and other conditions. In 1942 Ellis published an analysis of 600 cases of 'Bright's disease' which separated glomerulonephritis into two main types. The term 'Bright's disease' was interpreted as covering the same pathological lesions as glomerulonephritis, the diffuse glomerulonephritis of Volhard and Fahr. Ellis suggested that glomerulonephritis could be divided into two groups which, to avoid complicated terminology, he called types 1 and 2. It was thought that there was not necessarily any aetiological similarity of the two types, nor was it thought that type 1 progressed through type 2 to a chronic glomerulonephritis. Type 1 implies a typical acute nephritis, with hypertension, oedema, mild nitrogen retention, and haematuria, usually

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following an acute streptococcal infection; the large majority of cases heal completely, a few patients die of renal failure in the early stages, and in some patients chronic glomerulonephritis develops. Type 2 nephritis characteristically presents a nephrotic syndrome, with generalized oedema, heavy proteinuria, decreased plasma albumin, and raised plasma-cholesterol concentration; hypertension, raised blood-urea levels, and macroscopic haematuria are usually not found at the outset, nor is there usually a history of preceding infection. The majority of such cases eventually progress to chronic renal failure. Clinically, in the early stages, these two diseases can readily be separated, both by physical signs and by laboratory investigations. As type 2 progresses, this separation may become increasingly difficult, more severe glomerular involvement reducing renal excretory function, with resultant nitrogen retention, and hypertension may also appear. Although to both the clinician and the pathologist there is no doubt of the existence of these two types in their early, pure forms, a reluctance to accept this classification has increased rather than decreased since Ellis's paper in 1942, largely because of cases seen *post mortem* in which the correlation of histological changes and clinical course do not allow a clear allocation to either type.

In the course of the last two years we have had the opportunity to study patients with evidence of renal involvement with the aid of renal biopsy, performed by the percutaneous route, using the method described by Kark and Muehrcke (1954). We have been struck by the relatively frequent finding of a focal type of glomerulonephritis, occurring in 13 of a total of 100 biopsies. From correlation with the clinical findings and course of the disease in these patients, we believe that the Ellis classification falls short in that focal glomerulonephritis has not had sufficient importance attached to it. Post-mortem histological findings in the kidney in glomerulonephritis in the main represent either very severe or advanced chronic changes, and it is not surprising that it has not been possible from such material to recognize the existence of a further type. Although Ellis (1942) and Volhard and Fahr (1914) recognized focal glomerulonephritis, it was thought to be a relatively rare condition, seen by the pathologist only as an incidental finding. The only clinical abnormality was said to be the presence of red cells and protein in the urine, usually occurring at the height of an infection. The condition was considered benign, although the diagnosis was inevitably presumptive, and depended on the absence of any other findings consistent with the presence of a diffuse glomerulonephritis. Ellis (1942) briefly mentioned 35 patients, of whom 11 had repeated attacks of haematuria. In two of these patients albuminuria persisted between the attacks, death occurring many years later in renal failure; no pathological findings were discussed. In the present paper the clinical and histological findings in 13 cases of focal glomerulonephritis are presented. The difficult diagnosis in some cases from either type 1 or type 2 is apparent. In the great majority of patients urinary abnormalities have persisted for many months after the onset and, had renal biopsies not been obtained, their condition would almost certainly have been labelled as latent or chronic forms of type 1 or 2 nephritis.

Case Histories

Table I gives a summary of the main features when the patients were first seen, and Table II gives brief follow-up details for each patient.

TABLE I

Main Clinical Features at Time of Presentation

Patient	*Age and sex*	*Changes in urine*	*Highest blood-pressure in early stages (mm.Hg)*	*Highest blood-urea level in early stages (mg./100 ml.)*	*Oedema*	*Rash*	*Interval between time of first known renal involvement and renal biopsy (weeks)*
1	55 M	Protein +++ Red cells + Casts +	150/90	98	++	+	12
2	43 M	Protein +++ Red cells +++	180/140	38	0	+	6
3	32 F	Protein ++ Red cells ++ Casts +	110/70	100	0	+	20
4	68 M	Protein + Red cells + White cells +	160/95	23	Face and eyelids	+	3
5	19 M	Protein +++	180/90	42	Face only	+	12
6	44 F	Transient episode of protein +	140/80	34	0	+	10
7	19 F	Protein ++ Red cells + White cells +	130/84	48	0	+	8
8	55 M	Protein ++	150/90	55	+	0	52
9	47 M	Protein + Red cells ++	150/100	100	0	0	12
10	34 M	Protein ++ Red cells ++	185/110	40	0	0	12
11	55 M	Protein ++ Red cells ++	210/120	65	+++	0	6
12	35 M	Protein ++ Frank haematuria	150/105	150	+++	+	4
13	20 M	Protein +++ Red cells +++ White cells ++	160/100	35	0	0	8

Patient No. 1, a man aged 55, in whom the Schönlein-Henoch syndrome followed an infected thumb, with a transient nephrotic syndrome, has been fully reported elsewhere (Case 15, Joekes, Heptinstall, and Porter, 1958).

Patient No. 2, a man aged 43, was admitted to hospital on 27.3.57. Four weeks previously he went to his doctor with slightly painful swelling of his ankles; some purpura was noticed. Four days later he developed colicky abdominal pain, which lasted intermittently for three days; no blood was seen in the stools. At this time he also had aching pains in the wrists and elbows, and these persisted until his admission to hospital. The patient was unaware of any precipitating factor in his illness. He was first seen as an out-patient on 18.3.57, and again on 21.3.57; in these three days his weight fell from 12 st. 13 lb. to 12 st. 6 lb., presumably by loss of oedema fluid. There was no relevant past history.

On examination he looked healthy. There was fading purpura on the legs, and limitation of movement of the wrists and elbows, but no articular swelling was detected. The blood-pressure was 180/140. Venous pressure was not raised;

there was no oedema. The urine contained protein +++ (6 g. per litre), and red blood-cells +++. The blood urea was 38 mg. per 100 ml., haemoglobin 11·8 g. per 100 ml., white cells 15,000 per cu. mm., platelets 300,000 per cu. mm., and erythrocyte sedimentation 48 mm. in one hour; plasma proteins were 6·84 g. (albumin 4·2 g.) per 100 ml. The antistreptolysin-O titre was less than 200 units. Creatinine clearance was 133 ml. per minute. No L.E. cells were seen in the peripheral blood.

TABLE II

Follow-up Details

Patient	*Age and sex*	*Time interval from renal biopsy to last follow-up (weeks)*	*Urine*	*Blood urea (mg./100 ml.)*	*Blood-pressure*	*Follow-up details*
1	55 M	55	Protein + White cells +	55	130/80	Entirely symptomless. Serum proteins 6·1 g., albumin 2·7 g./100 ml. No oedema
2	43 M	33	Protein ++ Red cells +++	32	126/84	Very well. Blood-pressure rose to 170/100 when serpasil was stopped (resumed before final follow-up)
3	32 F	97	Protein 0	24	136/76	Very well
4	68 M	22	Protein trace	30	150/100	Recurrence of few purpuric eruptions on one leg
5	19 M	44	Protein + (1 g./24 hrs.)	32	126/80	Very well. Full work. Plasma protein and cholesterol normal
6	44 F	62	Protein faint trace	36	180/110	Prednisone stopped on rise of blood-pressure, which had not exceeded 145/95 till May 1958
7	19 F	16	Protein 0	24	120/85	Maintained on prednisone
8	55 M	..	..	..	..	No follow-up possible
9	47 M	60	Protein + Red cells ++ Casts +	76	190/115	Still taking prednisone, and 10 mg. mecamylamine t.i.d. Few fundal haemorrhages and exudates
10	34 M	60	Protein +++	25	135/95	Very well. 1 stone weight lost in last six months
11	55 M	50	Protein 0	42	135/80	No oedema. Very well. Total plasma proteins 7·8 g./100 ml.
12	35 M	14	Protein 0	40	140/80	Well and has returned to work
13	20 M	37	Protein ++ Red cells ++ Casts +	55	150/110	Taking long-term steroids. Recurrence of repeated small haemoptyses for 10 weeks. Some headaches, but generally well. Haemoglobin 13·3 g./100 ml.

The blood-pressure was controlled first with mecamylamine, and then with serpasil, remaining in the range 130/80 to 158/100 until the patient's discharge on 29.5.57. Prednisone was given for three weeks, and then discontinued. The urine still contained many red cells, and about 2 g. protein per litre, on his discharge. Renal biopsy was on 10.4.57.

Follow-up. He was seen on several occasions as an out-patient, the last occasion being 25.11.57, when he was very well; there was no recurrence of any

symptoms, and no abnormal physical signs. The blood-pressure was 126/84 (on serpasil); the urine contained many red cells, and protein ++. The blood urea was 32 mg. per 100 ml. when last recorded.

Patient No. 3, a woman aged 32. In November 1955 she had septic tonsillitis, and was admitted to hospital and treated with sulphonamides. Fourteen days later she developed joint pains and stiffness, and a generalized purpuric eruption; at this time proteinuria and microscopic haematuria began. Three weeks after her first admission a heavy *Bact. coli* urinary infection was found; sulphadimidine was started, but after receiving only 1 g. the patient had a gross exacerbation of purpura, with abdominal cramps, macroscopic haematuria, and oliguria. The blood-urea level rose to over 100 mg. per 100 ml. in December 1955, but had fallen to 50 mg. per 100 ml. by March 1956. Protein loss in the urine was fairly heavy (3 to 5 g. per 24 hours). There was no hypertension or oedema. Treatment with antihistamine drugs and cortisone was given from the time of the exacerbation which followed sulphadimidine administration.

In April 1956 the patient was first seen by one of the authors. On examination she looked healthy. A fine purpuric eruption was seen on the dorsum of both feet, and on an area of the abdomen where adhesive tape had been applied. The blood-pressure was 110/70. Venous pressure was not raised, and there was no oedema. The fundi were normal. The urine contained protein, 300 mg. per 100 ml. (4·2 g. in 24 hours). Renal biopsy was on 10.4.56.

Follow-up. On 11.5.57 the patient remained very well. There were no abnormal physical signs. The blood-pressure was 140/70. The urine contained a small amount of protein; the centrifuged deposit was sparse, and consisted of vaginal epithelial cells. The blood urea was 31 mg. per 100 ml., serum cholesterol 238 mg. per 100 ml., and total plasma proteins 6·9 g. per 100 ml. Urea clearance was 60 ml. per minute. The urine contained protein, 10 to 22 mg. per 100 ml. (400 mg. in 24 hours). In April 1958 the patient was very well. There was no protein in the urine. The blood urea was 24 mg. per 100 ml., and the blood-pressure 136/76.

Patient No. 4, a man aged 68, was admitted to hospital on October 1, 1957. Four days previously he went to his doctor because of cough and diarrhoea, and two days later developed purpuric spots on the legs and arms, and swelling of the face, with some watery discharge from the eyes. The following day some exfoliation of the skin began in areas involved in the rash. There had been no abdominal pain or blood in the stools, nor had there been any joint pains. There was no relevant past history.

On examination a scaling dermatitis was seen on the face and hands, with some swelling of the face and eyelids, and mild bilateral conjunctivitis. The blood-pressure was 160/95. There was a fine, generalized purpuric rash, most profuse on the lower legs. The Hess test was positive. A few scattered expiratory rhonchi were heard over the lungs. There was no oedema of the legs or trunk.

The urine contained protein +; the sediment showed some red cells, white cells, and occasional casts. A catheter specimen was sterile. The haemoglobin was 90 per cent. (13·3 g. per 100 ml.), white cells 6,200 (polymorphs 4,200) per cu. mm., and erythrocyte sedimentation 45 mm. in one hour. The bleeding time was 2 minutes 20 seconds, clotting time 3 minutes 40 seconds, and platelets 142,000 per cu. mm. The blood urea was 23 mg. per 100 ml., and serum cholesterol 90 mg. per 100 ml. No L.E. cells were found in the peripheral blood. Renal biopsy was on 16.10.57.

Follow-up. In March 1958 he had had a recurrence of purpura on one leg. The urine contained a faint trace of protein, no cells, and no casts. The blood urea was 30 mg. per 100 ml., and the blood-pressure 150/100.

Patient No. 5, a man aged 19, had a transient nephrotic syndrome associated with very limited purpura and prolonged, but diminishing, proteinuria. This case has been fully reported elsewhere (Case 16, Joekes, Heptinstall, and Porter, 1958).

Patient No. 6, a woman aged 44, with chronic lupus erythematosus and evidence of general systemic involvement after 20 years, has been fully reported elsewhere (Everall, Heptinstall, and Joekes, 1958).

Patient No. 7, a woman aged 19, was admitted to hospital on 4.11.57. Three weeks previously she developed a rash on the face after the application of a make-up lotion. On the morning following the first application a bright erythema appeared on her face and forehead. That evening the same lotion was again applied, and the following day the rash was worse. She felt perfectly well generally until one week later, when she began to feel ill and shivery. A few days before her admission the rash spread to the trunk and arms. Two years previously she had had contact dermatitis from a wrist watch.

On examination she was confused and restless, with generalized choreiform movements. There was a vivid erythematous rash on the forehead and face, neck, chest, and hands and forearms, with haemorrhagic bullae on the face and chest. The blood-pressure was 130/80. There were no other abnormal physical signs. The urine contained protein ++. Many L.E. cells were found in the peripheral blood. The blood urea was 45 mg. per 100 ml. The erythrocyte sedimentation rate was 55 mm. in one hour, haemoglobin 11·9 g. per 100 ml., white cells 10,000 per cu. mm., and platelets 200,000 per cu. mm. Renal biopsy was on 31.12.57.

The patient was very gravely ill, with cerebral involvement, for three weeks, but then gradually improved and made an excellent recovery. Intensive steroid therapy was used, and she continued to receive prednisone as an out-patient. The blood-urea level never rose above 48 mg. per 100 ml., and became normal before her discharge. There was no hypertension. She was last seen in May 1958. She was very well, and intended to get married in one month.

Patient No. 8, a man aged 55 years. A case of the nephrotic syndrome, possibly with systemic lupus erythematosus. Follow-up was inadequate. This patient was reported by Joekes, Heptinstall, and Porter (1958) (Case 14).

Patient No. 9, a man aged 47, was admitted to hospital with a febrile illness in October 1956. There was clinical evidence of a patchy pneumonia, and the urine contained small amounts of protein with considerable numbers of red and some white cells. He was treated with antibiotics for pneumonia, with general improvement and settling of the temperature. Microscopic haematuria continued, and there was biochemical evidence of renal failure, the blood urea remaining in the range 70 to 100 mg. per 100 ml. The only symptoms during the next four months were more or less continuous aching in both renal angles. With continuing haematuria and renal failure, a renal biopsy was performed on 25.1.57. He was treated with long-term prednisone. By December 1957 his blood-pressure had risen from the original 150/100 to 200/130, and fundal exudates were present.

Follow-up. In September 1957 the patient was permanently invalided from the Services, with a blood-urea level of 150 mg. per 100 ml. He felt well, however, and in March 1958 his blood urea was 76 mg. per 100 ml.; in spite of hypotensive therapy with mecamylamine his blood-pressure was 190/115, and changes were still present in the ocular fundi.

Patient No. 10, a man aged 34. Routine medical examination in December 1956 revealed heavy proteinuria. In November 1956, while in Nigeria, he had had a febrile episode, with pain across the small of the back; at the same time there was a red, inflamed area round a scratch on one calf. The patient thought he was having an attack of malaria. A diagnosis of 'blood poisoning' was made, and he was treated with a short course of aureomycin. The patient thought his urine was scanty and dark, but it was not examined at the time, although he drew attention to it. He remained perfectly fit for work, but was referred to Dr. C. A. Young on account of persistent proteinuria, when on annual leave in this country, in March 1957. On examination he looked well, with a good physique, and there were no abnormal physical signs. The blood-pressure was 130/80, rising to 185/110. The blood urea was 40 mg. per 100 ml., total serum proteins 7·6 g. per 100 ml., and serum cholesterol 230 mg. per 100 ml. The erythrocyte sedimentation rate was 7 mm. in one hour. Renal biopsy was on 12.3.57.

Follow-up. In August 1957 he appeared well, with no abnormal physical signs, but proteinuria +++. In May 1958 he remained very well. He had lost weight in the last six months.

Patient No. 11, a man aged 55, had a transient nephrotic syndrome, with complete remission. This case was fully reported by Joekes, Heptinstall, and Porter (1958) (Case 17).

Patient No. 12, a man aged 35, was admitted to hospital on 15.2.58. On 4.1.58 he had developed irritation of the left forearm, and soon after noticed red raised spots on both arms and legs. No purpuric element was present. Some of the spots became infected. Penicillin powder was applied to the infected spots, and 0·5 per cent. hydrocortisone lotion to the remainder of the rash, a total of 150 ml. being used. The rash subsided, but on 18.1.58 he developed a fairly gross oedema involving the legs, thighs, and face; this lasted for two weeks, and then gradually subsided. Painless haematuria was first noticed on 10.2.58, when the oedema had disappeared. There was no relevant past history. There had been no preceding sore throat. At no time had there been dyspnoea or cough.

On examination he was a healthy-looking man. There was faint brownish discoloration in the areas of fading rash on the arms and legs. Moderately enlarged glands were present in the axillae and groins. There was no oedema. Venous pressure was not raised. The pulse rate was 80, and the blood-pressure 150/105. The haemoglobin was 13·6 g. per 100 ml., white cells 6,600 per cu. mm., and erythrocyte sedimentation 8 mm. in one hour. The blood urea was 53 mg., and total plasma proteins 5·7 g. (albumin 2·9 g.) per 100 ml. A midstream specimen of urine was sterile; proteinuria was ++, and the sediment consisted of white cells, red cells, and a large amount of debris. The serum cholesterol was 225 mg. per 100 ml. On 6.3.58 the antistreptolysin-O titre was 90 units.

The patient at no time felt unwell. The blood-pressure fell to normal levels in a few days, and remained normal. The macroscopic haematuria present on admission had disappeared after three days, but returned for one day on 18.3.58. On 26.2.58 the blood urea was 120 mg. per 100 ml., and the urea clearance

15 ml. per minute. Plain X-rays of the abdomen showed kidneys of normal size and shape. Renal biopsy was on 11.3.58.

Renal function continued to show fairly gross impairment, with a blood-urea level of 150 mg. per 100 ml. on 31.3.58. By 17.4.58 it fell to 70 mg. per 100 ml., and he was discharged free of symptoms, and with no abnormal physical signs except for moderate proteinuria. The latest follow-up observations are shown in Table II.

Patient No. 13, a man aged 20, had had haemoptysis, which started in September 1956 and continued intermittently for over six months. Full pulmonary investigations revealed no abnormality. In June 1957 proteinuria was first discovered; the urine sediment contained many red cells, and some white cells and casts. After his admission there was no evidence of renal failure. Renal biopsy was on 12.8.57.

Follow-up. He continued to receive prednisone, and felt well. The findings in the urine were unchanged. The blood-pressure remained slightly raised. The blood-urea level was within normal limits until his last attendance as an out-patient in April 1958, when it was raised. Details are given in Table II.

General Description of Pathological Findings

Kidney tissue was obtained by percutaneous needle biopsy; serial sections were cut at 5 μ thickness, and all mounted six per slide. Every fourth slide was stained with haematoxylin and eosin, and intervening slides with haematoxylin and van Gieson's mixture, periodic-acid-Schiff reagent, and methyl violet; in some cases other special stains were used. In certain cases material was fixed in cold acetone, and prepared to show alkaline phosphatase by the coupling azo dye method. In some instances additional tissue was taken for bacterial culture. In two cases culture was attempted from washings of the biopsy needle. All 13 cases showed the features characteristic of focal glomerulonephritis, and the types of lesion found had the following appearances. It should be emphasized that 'focal' is used to mean that only a proportion of the glomeruli are abnormal, while 'local' is used to denote a change affecting only a part of a given glomerulus. In all cases only a certain number of glomeruli, varying from one-quarter to two-thirds of the glomeruli seen, showed abnormalities, the remainder being absolutely normal.

The affected glomeruli frequently showed cellular proliferation of both endothelial and epithelial cells, this increase usually affecting only a part of the tuft (Plate 24, Figs. 1 and 2), but sometimes affecting the tuft diffusely (Plate 24, Fig. 3). This localized or eccentric involvement of the tuft was a prominent feature of the group. In some instances the proliferation in the tuft was accompanied by an overgrowth of epithelial cells lining Bowman's capsule. Adhesions between the tuft and Bowman's capsule were usually present. Certain cases (Nos. 2, 6, 7, 9, and 10) showed localized eosinophilic areas in some of the tufts, representing either an area of necrosis (Plate 24, Fig. 4) or, in others, an intracapillary thrombosis with eosinophilic thickening of the basement membrane. Hyalinization or fibrosis of the glomerular tuft was a frequent finding, sometimes affecting the whole tuft, but in other cases involving only one or

two lobules, or even affecting merely the periphery of one or more lobules (Plate 25, Figs. 5, 6, and 7). Organized crescents were sometimes seen (Plate 25, Fig. 8).

Tubular changes were inconstant, but most cases showed a focal tubular atrophy, and eosinophilic casts were usually present in the tubules. Apart from loss in atrophic proximal convoluted tubules, there were no abnormalities in the alkaline-phosphatase pattern. Interstitial tissue sometimes showed small collections of lymphocytes, and sometimes patchy areas of fibrosis. Some specimens showed intimal thickening of arteries and hyaline changes in arterioles, but in most cases the vascular changes were insignificant. No necrotizing arteriolar or arterial lesions were seen.

No organisms were grown from the ground-up tissue in the six instances in which such material was taken, and no growth was obtained from washings of the needle after biopsy in two additional cases.

Table III summarizes the more important features.

TABLE III

Main Histological Changes

Case number	*Number of glomeruli seen*	*Proportion of glomeruli affected*	*Cellular proliferation in tuft*	*Cellular proliferation of cells lining Bowman's capsule*	*Adhesions between tuft and Bowman's capsule*	*Necrosis or intra-capillary thrombosis in tufts*	*Eccentric hyalinization or fibrosis of tufts*	*Bacterial culture of renal tissue (*culture of needle washings only)*
1	18	One-third to one-half	+	−	+	−	+	Negative
2	14	One-half	++	+	+	+	+	..
3	24	One-half	++	+	+	−	+	*Negative
4	36	One-third to one-half	+	+	+	−	+	Negative
5	27	One-third	+	+	+	−	+	Negative
6	24	One-quarter	++	+	−	+	−	..
7	32	One-half	+	+	+	+	+	..
8	18	One-third to one-half	+	−	+	−	+	*Negative
9	28	Two-thirds	+	+	+	+	+	Negative
10	22	One-quarter	+	+	+	+	+	Negative
11	28	One-half	+	+	+	−	+	Negative
12	20	One-quarter	+	+	+	−	+	..
13	30	One-half	++	+	+	−	+	..

Clinical Assessment

Apart from the histological appearances in the renal biopsy material, the only factor common to all the patients has been a urinary abnormality. In all cases proteinuria was present, although in one (patient No. 6) it was absent at the time of biopsy. Similarly, an abnormal urinary excretion of cells, predominantly red cells in most cases, was found, although in patient No. 8 it could be detected only by special counting technique (Houghton and Pears, 1957). Although renal biopsies were obtained several weeks after the first known evidence of renal involvement, there had not been any clinical evidence which suggested the classical picture of an acute type 1 glomerulonephritis. The most striking clinical association with the histological picture of focal glomerulonephritis in these patients has been the presence of a condition usually accepted as some form of sensitization reaction. Three clear cases (Nos. 1, 2, and 3) and two less certain cases (Nos. 4 and 5) of Schönlein-Henoch purpura, and two cases of proven systemic lupus erythematosus (Nos. 6 and 7), may all be clinical conditions depending on a sensitization reaction. Table IV shows for each patient

any infective episode or evidence of a sensitization phenomenon which preceded or coincided with the known onset of renal involvement. The antistreptolysin-O titre was not raised in those cases in which it was estimated. The commonest form of clinical presentation referable to the renal involvement showed many similarities to that seen in acute Ellis type 1 glomerulonephritis: oedema, hypertension, haematuria, and nitrogen retention. It is a striking fact, however,

TABLE IV

Relationship of Infection or Possible Sensitization Phenomena to Onset of Renal Involvement

Patient number	*Infective episode*	*Interval to known renal involvement*	*Evidence of sensitization reaction*	*Diagnosis other than focal glomerulonephritis*
1	Septic thumb	10 days	..	Schönlein-Henoch syndrome
2	..	..	..	Schönlein-Henoch syndrome
3	Tonsillitis	14 days	Exacerbation of signs and symptoms following sulphonamides	Schönlein-Henoch syndrome
4	Respiratory infection and diarrhoea	> 4 days	Purpura and exfoliative dermatitis	..
5	..	..	Purpura	..
6	..	..	Systemic lupus erythematosus	Systemic lupus erythematosus
7	..	..	Acute systemic lupus erythematosus following use of cosmetic lotion	Systemic lupus erythematosus
8	..	..	..	Systemic lupus erythematosus ?
9	Pneumonia	..	..	Polyarteritis nodosa ?
10	Inflammatory lesion on calf	< One month	..	..
11	Sore throat and conjunctivitis	< 4 weeks	..	..
12	Rash with infective element	< 4 weeks	Rash thought to be urticarial	..
13	..	..	..	Primary pulmonary haemosiderosis

that the venous pressure has never been found raised. A further difference has been a heavy proteinuria persisting over many weeks or months, and in five patients (Nos. 1, 5, 8, 11, and 12) a nephrotic syndrome was present at some time.

Table II sets out some of the follow-up findings at the time when each patient was last seen. The nephrotic syndrome had been transient in all the five patients who had it, and in the four patients who were followed up the proteinuria had diminished greatly, completely disappearing in two cases (Nos. 11 and 12). The follow-up period is too short for any long-term assessment of the clinical course of the 13 patients. In systemic lupus erythematosus, once evidence of renal involvement is established, a progressive lesion with increasing kidney damage is thought to be the rule. In the present series, although the histological appearances in patients without lupus erythematosus are similar to

those seen in patients with that condition, the clinical evidence so far points to a more favourable course in some of the former. In Case 3, for example, the urinary abnormalities persisted for more than 18 months, and the patient eventually appeared to recover completely.

Discussion

The finding of the changes characteristic of focal glomerulonephritis in 13 biopsies out of 100 performed for a variety of conditions is of considerable interest from the point of view of the evolution of pathological processes in the kidney. The high incidence can be explained in part by the inclusion of such conditions as systemic lupus erythematosus, in which the focal nature of the lesion is well known from both post-mortem (Klemperer, Pollack, and Baehr, 1941) and renal biopsy material (Muehrcke, Kark, Pirani, and Pollak, 1957). A further patient was suspected clinically of having polyarteritis nodosa, another condition in which focal lesions in glomeruli are well recognized.

In the standard texts dealing with renal diseases there is surprisingly little information concerning focal glomerulonephritis. Broadly speaking, two main groups are described. The first comprises those cases in which a patient, during the course of some infective process caused by streptococci, pneumococci, or other organisms, develops blood, protein, and casts in the urine. This type of lesion occurs at the height of the infection, as opposed to classical acute glomerulonephritis, in which there is a latent interval between the onset of the infection and the presentation of renal symptoms. Fishberg (1954) considered that the type of lesion occurring at the height of infection, which he described as being characterized by certain glomeruli showing endothelial proliferation with leucocytes in slight excess, was due to direct bacterial invasion. Allen (1952) disagreed with this interpretation and, although admitting there is a group in which suppurative lesions occur due to lodgement of bacteria, held that the thesis of Fishberg could not be maintained, and that the glomerular lesions were allergic in nature. The second main group is that of focal embolic glomerulonephritis, the renal lesion of subacute bacterial endocarditis. In this condition scattered glomeruli show an eosinophilic focus in a portion of the tuft, representing intracapillary thrombosis, often associated with necrosis of the capillary basement membrane. Cellular proliferation is often found, both in the affected tuft and sometimes involving the adjacent epithelial lining of Bowman's capsule. The cause of this lesion has been disputed; Löhlein (1910), Baehr (1912), Fahr (1925), and Bell (1932) considered it to be caused by the lodgement of minute infected emboli derived from the vegetations of the heart in subacute bacterial endocarditis. Longcope (1916), however, disagreed with this explanation, and considered the lesion to be of an allergic nature. A further piece of evidence against the embolic nature of such glomerular lesions is provided by a case of Bain, Edwards, Scheifley, and Geraci (1958), in which typical kidney lesions were found in the presence of bacterial endocarditis confined to the tricuspid valve. Additional features in the kidney of focal embolic glome-

rulonephritis are the presence of fibrous lesions in scattered glomeruli, having an eccentric position in the tuft in the same way as the lesion just described. These lesions are regarded by most observers as a healed form of the acute lesion, although Bell (1932) considered them to bear no relationship to the latter. In addition there is sometimes a diffuse proliferative lesion of all glomeruli; Christian (1942) put the incidence of cases showing this change as high as 80 per cent. The lesions of focal embolic glomerulonephritis are described at some length because of their similarity to some of the findings in the present series. In addition to the two main groups of focal glomerulonephritis just described, there are isolated reports of the lesion being found in drug hypersensitivity.

The lesions most frequently found in the present series are cellular proliferation in glomerular tufts, and eccentric areas of hyalinization in other tufts with adhesions. Cellular proliferation sometimes affected the whole of the tuft, but was more usually confined to a single lobule. This is in distinction to the lesion of diffuse glomerulonephritis, in which the proliferative lesion, besides affecting all the tufts, affects individual tufts diffusely. Polymorphs were usually absent in the present series, and when present were scanty. Epithelium lining Bowman's capsule frequently showed proliferation, and on occasions fully formed crescents were present, while in certain cases there were fibrotic crescents. This type of epithelial proliferation almost invariably occurred in glomeruli showing changes in the tufts. The frequent presence of hyalinized areas at the periphery of individual tuft lobules probably represents a healed lesion, as its incidence was greatest in cases showing least cellular proliferation, and was least in those with most proliferation. These lesions are reminiscent of those found in focal embolic glomerulonephritis, which Bell (1932) called the fibrous type of lesion as opposed to the fresh type characterized by intravascular thrombosis with or without adjacent necrosis. In favour of the hyalinized areas representing a healed lesion in our material is the frequent finding of adhesions between the affected area and Bowman's capsule. In five of the cases intravascular thrombosis of capillary tufts was found, sometimes associated with necrosis. One of the five patients under discussion was suspected of having polyarteritis nodosa, while two were proved to have systemic lupus erythematosus. All instances of this change showed a pronounced proliferative element in the tuft, although not necessarily in the tuft with necrosis. This type of change resembles the fresh glomerular lesion of subacute bacterial endocarditis, but there was nothing suggestive of this condition in any of the five cases under discussion. Bacterial culture of ground-up renal tissue was negative in the cases in which such material was taken. The same type of lesion, however, frequently occurs in polyarteritis nodosa of the so-called microscopic type (Davson, Ball, and Platt, 1948). The lesion in polyarteritis is especially relevant to some of the arguments in relation to nomenclature in the present paper. One of the cases (No. 9) showed a histological picture consistent with this diagnosis, based mainly on the presence of focal and local fibrinoid necrosis in glomeruli in the absence of hypertension of any severity. In this case the renal lesions consisted not only of capillary necroses, but local cellular proliferation in the tufts and epithelial

crescent formation were also present. Of the nine cases of Davson, Ball, and Platt's group A, the so-called microscopic type, four showed cellular proliferation in the glomerular tuft, and seven showed capsular proliferation; their Case 6 is of particular interest in that the changes of fibrinoid necrosis were less marked than the proliferative changes. Although these authors did not class the lesion of polyarteritis as a focal glomerulonephritis, their description in some cases unequivocally falls within the broad meaning of the term. They compared the changes found with those of focal embolic glomerulonephritis, but concluded that the absence of bacterial endocarditis, and the presence of typical lesions of polyarteritis nodosa in other organs, served to eliminate the diagnosis of embolic glomerulonephritis. In polyarteritis two types of focal glomerular changes may be present: the proliferative change places the lesion in the group of focal glomerulonephritis, the fibrinoid necrosis representing vascular damage which is so characteristic of polyarteritis. While it is tempting to explain the necrotizing glomerular changes in the cases under discussion on the basis of hypersensitivity, by analogy with polyarteritis nodosa, it should be remembered that similar changes may also be found in malignant hypertension. Even in polyarteritis nodosa the possibility that the necrotizing lesions in glomeruli may be embolic in origin should not be lightly dismissed (Rich, 1956). Further strength is added to this view by the demonstration of similar lesions by Muirhead, Booth, and Montgomery (1957), who produced them in dogs by the injection of autolysed muscle into the renal artery. In the present series of cases, with but two exceptions, there was no considerable elevation of blood-pressure, nor was there any evidence of scleroderma, another condition in which necrotizing glomerular changes are found. Patient No. 2 had a maximum diastolic blood-pressure of 140 mm. Hg, and in one glomerulus there was a small eosinophilic area representing intravascular thrombosis, with blurring of the adjacent capillaries. Though this may have been a consequence of the high blood-pressure, it is unlikely because of the absence of arteriolar necroses.

The proliferative glomerular changes described in our cases range from quite small areas of local epithelial and endothelial cell collections in one lobule of a glomerulus to much larger areas, often associated with proliferation of adjacent cells lining Bowman's capsule. We believe that the term focal glomerulonephritis should be restricted to cases showing an essentially proliferative type of glomerular change, at some stage of its evolution. This point is emphasized in order not to include all examples of focal and local glomerular change. Both in amyloidosis and in diabetic glomerulosclerosis focal and local deposits of eosinophilic material are found in the kidney. It should, however, be stated that a similar glomerulitis may be found in association with pyelonephritis, and this is a condition that cannot be completely ruled out by renal biopsy. We have seen occasional glomeruli showing proliferative changes in biopsy specimens from patients with combined hypertension and pyelonephritis, and this change is frequently seen in autopsy material in cases of pyelonephritis with hypertension and renal insufficiency, having been called 'alterative glomerulitis' by Kimmelstiel and Wilson (1936). In the present series ground-up material

obtained by renal biopsy failed to produce any growth on culture in all six cases so investigated. Washings from the biopsy needle were negative on culture in two additional cases. While the latter cannot be regarded as altogether satisfactory evidence for the sterile nature of the kidney tissue, the six cases in which ground-up material was used demonstrate the absence of a generalized invasion by organisms.

Two main questions seem to arise. First, are the glomerular lesions, here described as a separate entity, possibly an unrecognized stage of type 1 glomerulonephritis? And secondly, what is the evolution and subsequent appearance of these lesions? The present authors have had the privilege of seeing in detail the renal biopsy material obtained by Hutt, Pinniger, and de Wardener (1958) from patients with the clinical diagnosis of acute glomerulonephritis. The histological picture is strikingly different from that described in the present series; there is an almost uniform involvement of glomeruli, and the predominantly endothelial proliferation and associated polymorphonuclear infiltration tend, on the whole, to be evenly spread through any one glomerulus. This is true whether the biopsy was taken at the height of the attack or during its resolution. In accordance with the experience of Hutt, Pinniger, and de Wardener, the present authors believe that acute diffuse glomerulonephritis (corresponding to Ellis type 1) has a distinct clinical picture, consisting of an acute generalized oedema, hypertension of a moderate order, a raised central venous pressure, and often a bradycardia or absence of tachycardia. In elderly patients the latter feature may be the first indication that some condition other than congestive cardiac failure is present. There seems to be no doubt that the cases in the present series are quite distinct histologically from acute type 1 glomerulonephritis. Nor is there any clinical evidence that the patients had, at some time before the renal biopsy, an attack of acute type 1 glomerulonephritis, if the diagnostic criteria described above are accepted.

The generally accepted view of the pathological changes of acute type 1 glomerulonephritis is that complete healing takes place in the great majority of patients in whom there is no evidence of rapid progression or of persistent renal involvement with urinary abnormalities. Such little evidence as has been obtained by renal biopsy bears this out. Hutt, Pinniger, and de Wardener (1958) reported an almost completely normal kidney five weeks after the onset of a typical attack; there had, however, been no previous biopsy for comparison. The present authors' experience in cases of acute type 1 glomerulonephritis is limited to four patients; in two of these a renal biopsy, eight weeks after the onset of a typical attack, showed an absolutely uniform appearance of the glomeruli, with only slight cellular proliferation and polymorphonuclear infiltration. In another patient, a man of 41, with many atypical clinical features in his acute attack, renal biopsy 10 weeks after the onset of the attack showed a typical active type 1 glomerulonephritis. In the preceding cases with the resolving lesions, and in the biopsies obtained earlier after the onset by Hutt, Pinniger, and de Wardener, there were no gross differences in the appearance of individual glomeruli, such as have been the rule in the present series of cases of

focal glomerulonephritis, and no suggestion that one might be seeing changes which represent various stages in a process from minor cellular proliferation to total hyalinization of glomeruli. The only case of severe acute type 1 glomerulonephritis in which a renal biopsy has been obtained by the present authors showed a histological picture very similar to that described in five patients by Brun, Hilden, Iversen, and Raaschou (1956), all of whom went on to develop oliguria and died. This group showed the changes typical of an acute type 1 glomerulonephritis, with the addition of focal changes of two kinds, a proportion of the glomeruli showing localized fibrinoid necrosis, and some showing crescent formation. Setting aside the occurrence of focal and local changes in some severe cases of type 1 glomerulonephritis, the evidence appears very good that the histological picture seen in the present series is quite distinct from classical acute type 1 glomerulonephritis.

The second question raised, regarding the evolution and subsequent appearance of the renal lesions, cannot be answered with certainty because of the lack of repeated biopsies. As mentioned before, the greater incidence of areas of hyalinization and fibrosis in the kidneys with the least cellular proliferation would indicate that these represent areas of healing. That areas of necrosis eventually become fibrotic cannot be doubted, because of the frequent findings of both types of lesion *post mortem* in the kidneys of patients with polyarteritis nodosa. It is reasonable to assume, by analogy with acute type 1 glomerulonephritis, that proliferative glomerular lesions can resolve completely. Several cases not included in the present series have been seen, some fatal, in which a renal biopsy showed widespread glomerular involvement not so uniform as in type 1 glomerulo-nephritis, yet sufficient to make it difficult to class the lesions as focal glomerulonephritis. The individual glomeruli, however, showed considerable variations, some containing obvious local lesions. It is possible that the pathological changes in these kidneys are fundamentally similar to those described in the present series, but on a more widespread scale. If it were accepted that a sensitization reaction is the basis of the renal lesion in focal glomerulonephritis, it would be reasonable to assume that the differing severities of lesion would be dependent on the size and duration of the antigenic stimulus. In the present series there is a wide range of severity of renal involvement, judged histologically and functionally. It is not difficult to believe that more severe renal involvement in a focal glomerulonephritis might affect the great majority of glomeruli, without having to suppose a difference in the nature of the lesion. With a prolonged antigenic stimulus, such as may be assumed in 'collagen disease', the renal lesion might be expected to be progressive, as opposed to that resulting from a single short-term antigenic stimulus. This problem cannot be clarified until serial biopsies are available from patients with severer lesions.

With the total number of reported renal biopsies now amounting to several hundreds, it is perhaps surprising that so few cases clearly presenting focal glomerulonephritis have been reported. The large majority of cases with focal, local proliferative lesions in the glomeruli have been in patients with the diagnosis

of lupus erythematosus; and even in this condition the proliferative lesion, which appears to the present authors as possibly the essential lesion, has received only scant attention, although Muehrcke, Kark, Pirani, and Pollak (1957), in reviewing renal biopsy material from 33 patients, briefly described small localized areas at the periphery of a glomerulus consisting of cellular proliferation. Parrish and Howe (1955), in a review of 100 renal biopsies, illustrated four glomeruli from one patient, one normal, one with a local lesion, one with capsular proliferation, and one with advanced hyalinization. No clinical details were given, except that the patient showed the signs and symptoms of acute renal disease, and no opinion was expressed as to the lesion in the kidney. Parkin, Rusted, Burchell, and Edwards (1955) described post-mortem findings in a group of seven patients, with a very uniform clinical picture dominated by repeated haemoptyses and renal failure progressing to a fatal outcome in a few months. The kidneys showed a form of glomerulonephritis, with about four out of every five glomeruli involved. There were local proliferative lesions in tufts, and capsular reaction; some glomeruli were completely hyalinized. It was thought that the lesion, both in the lungs and in the kidneys, represented some hypersensitivity reaction. This histological picture has many of the features which we think might be shown by a focal glomerulonephritis on a large scale. Patient No. 13 in the present series came under observation because of repeated haemoptyses, and showed a typical focal glomerulonephritis.

Bates, Jennings, and Earle (1957) have reported a group of 10 young male patients in whom proteinuria, and in seven cases gross haematuria, was associated, except in one patient, with pharyngitis. In none was a Group A haemolytic streptococcus isolated from the throat, nor was there any immunological evidence of a recent haemolytic streptococcal infection. In four of the nine patients from whom renal biopsy material was obtained the appearances were very similar to those seen in the present series, although in two cases both the first and second biopsies showed some local changes in all glomeruli seen. This report of acute nephritis unrelated to streptococcal infection is the only publication which appears to describe both renal histological changes and a clinical picture very similar in some respects to those described in the present paper. It is a striking fact that one of the patients described by Bates, Jennings, and Earle had a transient nephrotic syndrome, that in two there was transient hypertension, and that in one patient nitrogen retention occurred during the early stages of the glomerulonephritis. As in our series, urinary abnormalities persisted considerably longer in the majority of patients than is generally thought to occur in acute type 1 glomerulonephritis.

The factual diagnosis of focal glomerulonephritis in the present series by renal biopsy stands in contrast to the great majority of reports of cases with this pathological label, in which inevitably the diagnosis has been presumptive. The cases presented seem to prove that the long-established concept of focal glomerulonephritis as an entirely benign condition, and apparent only by the presence of haematuria, or seen pathologically only as a chance finding in a patient dead from some infection, is no longer acceptable. The natural history

of the various forms of glomerulonephritis should be reassessed on the basis of a certain histological diagnosis, obtained by renal biopsy, early in the course of the illness.

We are grateful to many colleagues for referring or allowing us access to cases (both those included in the present series and others) which have made our studies possible, and to Mr. A. Beasley for preparation of the histological sections. One of the authors (A. M. J.) was in receipt of a research grant from St. Mary's Hospital, London.

Summary

1. In a consecutive series of 100 percutaneous needle biopsies from patients with various forms of renal disease, 13 cases have been diagnosed histologically as focal glomerulonephritis.

2. The term 'focal' has been used to indicate that only a proportion of the glomeruli were affected by a pathological process. In all cases of focal glomerulonephritis the lesions were also, to some extent, local: that is, some affected glomeruli showed lesions in only part of the tuft.

3. The clinical picture associated with this pathological lesion has been very varied. Two of the patients, and possibly a third, had systemic lupus erythematosus, and in another patient the renal histological picture was compatible with polyarteritis nodosa. In the other patients the presenting features had many similarities to those seen with type 1 or type 2 glomerulonephritis, and without renal biopsy would certainly have received diagnostic labels other than focal glomerulonephritis.

4. It is concluded that a reassessment of the diagnosis of focal glomerulonephritis is due, and can be achieved only with the aid of renal biopsy studies.

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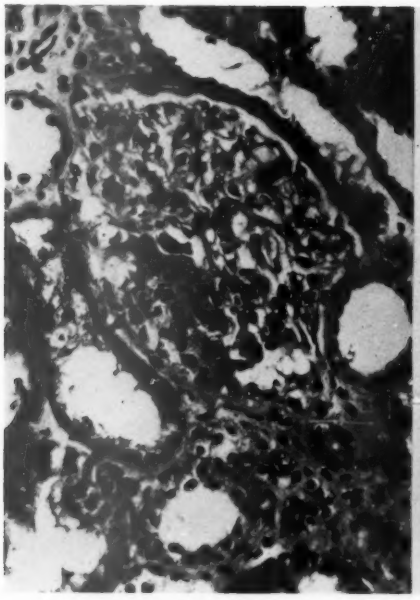

FIG. 1. Cellular proliferation affecting only part of the glomerular tuft (Case 10) (haematoxylin and eosin, ×320)

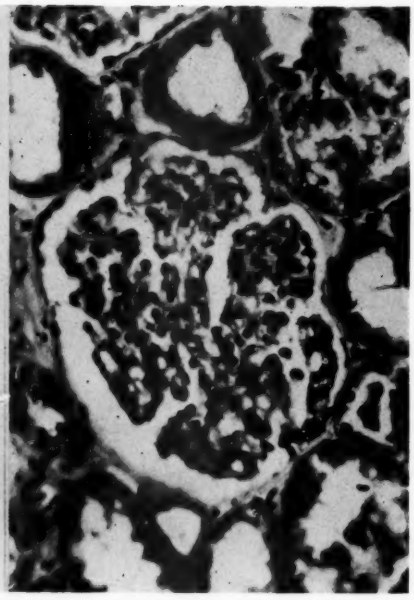

FIG. 2. Cellular proliferation predominantly affecting one lobule of the glomerular tuft (Case 3) (haematoxylin and eosin, ×320)

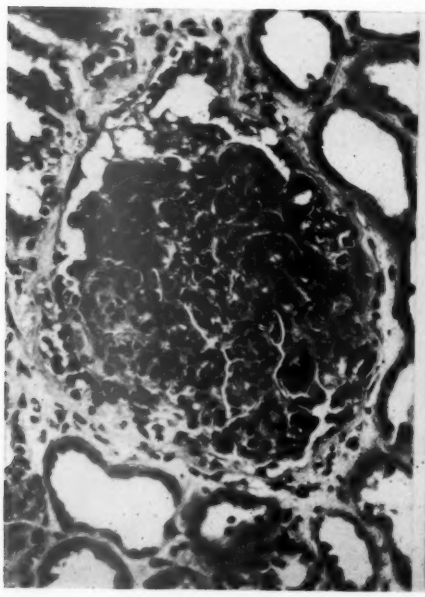

FIG. 3. Cellular proliferation affecting the whole of the glomerular tuft (Case 2) (haematoxylin and eosin, ×240)

FIG. 4. Glomerular tuft with a small local area of cellular proliferation and an area of necrosis (Case 9) (haematoxylin and eosin, ×240)

FIG. 5. Glomerulus with an area of fibrosis, and a localized area of cellular proliferation involving also the cells lining Bowman's capsule (Case 13) (haematoxylin and eosin, ×320)

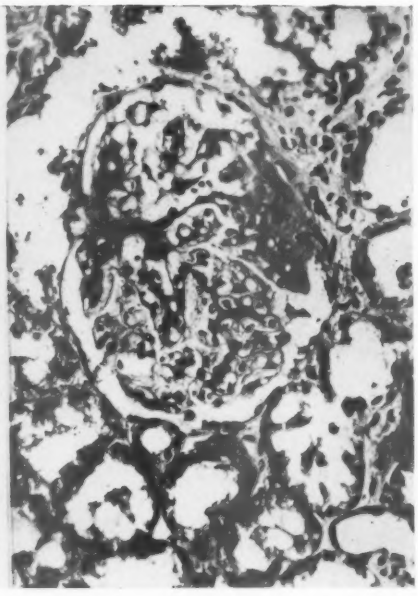

FIG. 6. Glomerulus with a localized hyaline area showing adherence to Bowman's capsule (Case 8) (haematoxylin and eosin, ×240)

FIG. 7. Glomerulus with one-half of the tuft hyalinized and adherent to Bowman's capsule (Case 9) (haematoxylin and eosin, ×320)

FIG. 8. Partially organized crescent with only minor proliferative changes in the glomerular tuft (Case 5) (haematoxylin and eosin, ×240)

616.44–008.61 : 616.12

THE NATURE AND PROGNOSIS OF HEART DISEASE IN THYROTOXICOSIS[1]

A Review of 150 Patients Treated with ^{131}I

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With Plate 26

The association of heart disease and thyrotoxicosis is widely known, and has been extensively recorded. Parry (1825) was the first to draw attention to the cardiac involvement in thyrotoxicosis, and described eight patients, the first seen in 1786, all of whom had exophthalmic goitre with palpitations, irregularity of the pulse, oedema, or cardiac enlargement. Other descriptions followed (Graves, 1835; von Basedow, 1840; Lockridge, 1879; Moebius, 1896). Although the occurrence of heart disease in thyrotoxicosis is well recognized, the precise relationship of hyperthyroidism to the genesis of the cardiovascular abnormalities has been a subject of considerable controversy throughout the present century. Some authorities have maintained that thyrotoxicosis alone can cause heart disease (Magee and Smith, 1935; Likoff and Levine, 1943; Griswold and Keating, 1949), while others have claimed that associated heart disease, such as coronary artery disease, hypertension, or rheumatic heart disease, is always present in such patients in addition to thyrotoxicosis (Willius, Boothby, and Wilson, 1923; Lahey and Hamilton, 1924; Hurxthal, 1928; Friedberg and Sohval, 1937). Many of the reports describing these differences of opinion were based on patients treated either by radical surgery or by antithyroid drugs. The former method of treatment excludes a number of patients with gross cardiac involvement in whom the operative risk was not considered justifiable. The use of antithyroid drugs, on the other hand, is possible in all these patients with severe heart disease, but is often associated with only incomplete and temporary control of the thyrotoxicosis. After the introduction of radioactive iodine by Hertz and Roberts (1942) a safe, radical, and permanent method of treatment of thyrotoxicosis was established, which could be used in all patients with thyrotoxicosis and heart disease, no matter how gross or incapacitating the latter might be.

Patients with cardiac involvement have been selected for detailed study from among a large group of thyrotoxic patients treated with ^{131}I. Many of these patients were gravely ill as a result of cardiac complications. They have been reviewed with particular reference to the course of the heart disease after a

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permanent cure of the hyperthyroidism has been attained. The aims of the present study, therefore, are to analyse the aetiological factors, cardiovascular manifestations, and prognosis in these patients. The role of thyrotoxicosis alone in producing heart disease is also considered in the light of the changes observed after treatment of the thyrotoxicosis, and of the autopsy findings in several cases.

Selection and Investigation of Patients

The investigation comprises a study of 462 thyrotoxic patients treated with ^{131}I during the period January 1949 to October 1956. The analysis is based on the condition of these patients in April 1958. The diagnosis of thyrotoxicosis was made principally on the clinical features and the results of ^{131}I tracer studies. The latter included measurement of the four-hour and 48-hour uptake by the thyroid gland, and the 48-hour plasma and protein-bound ^{131}I level as described by Wayne (1954). A correlation exists between the clinical assessment of the severity of thyrotoxicosis and the rate of uptake of ^{131}I on diagnostic tracer tests (Goodwin, Macgregor, Miller, and Wayne, 1951; Crooks, Murray, and Wayne, 1959). In the majority of cases the serum cholesterol was measured. In some cases further confirmation of the diagnosis was sought by estimations of basal metabolic rate, but often in patients with cardiac disease this test could not be satisfactorily performed owing to dyspnoea. In addition to the routine clinical examination of the cardiovascular system, electrocardiography with standard leads, unipolar limb leads (Goldberger, 1953), and chest leads (American Heart Association, 1938), and posterio-anterior chest X-rays, were carried out in all patients before treatment. In many instances this was supplemented by fluoroscopy and radiographs taken in the oblique positions. All the patients have been re-examined at frequent intervals after ^{131}I therapy. A full review of the cardiovascular features, including X-ray investigations and electrocardiography, has been carried out in all surviving patients showing any cardiac abnormality, at least one year after they became euthyroid. Wassermann and Kahn reactions were tested in all the patients. Only one positive reaction was found in a patient with hypertensive heart disease. The treatment of the thyrotoxicosis was with ^{131}I as described by Blomfield, Eckert, Fisher, Miller, Munro, and Wilson (1959). The aim was to give from 6,000 to 8,000 rads to the thyroid gland, the higher doses being intended for patients with severe cardiac involvement. In general, patients under the age of 40 years have been treated with ^{131}I only in exceptional circumstances.

Incidence of Heart Disease in Thyrotoxicosis

Circulatory disturbances are evident in most thyrotoxic patients, but signs such as tachycardia, peripheral vasodilatation, and systolic hypertension with a large pulse pressure, represent a response to excess of thyroid hormone rather than evidence of cardiac abnormality. In some patients, however, more definite features indicating heart disease are present. The patients in the present investigation have been divided into three main groups.

I. No definite clinical, radiological, or electrocardiographic evidence of cardiac involvement was found in this group.

II. In addition to the thyrotoxicosis, an unrelated condition affecting the heart was present. The abnormalities included coronary artery disease, hypertension, rheumatic valvular disease, pulmonary disease, and congenital defects. This group accordingly represents thyrotoxic patients with associated heart disease.

TABLE I

Thyrotoxic patients treated with ^{131}I, January 1949 to October 1956			462
Group I. Patients without cardiac involvement			312
Patients with cardiac involvement			150
Group II. With associated organic heart disease		86 (57%)	
Ischaemic heart disease	43		
Hypertensive heart disease	22		
Rheumatic heart disease	11		
Pulmonary heart disease	8		
Congenital heart disease	2		
Group III. No evidence of associated heart disease		64 (43%)	
Auricular fibrillation	48		
Congestive cardiac failure	26		
(*a*) with auricular fibrillation	23		
(*b*) with sinus rhythm	3		
Cardiomegaly alone	13		

III. In this group auricular fibrillation, congestive cardiac failure, or cardiomegaly confirmed radiologically was present, in the absence of clinical, radiological, or electrocardiographic evidence of any associated heart disease.

Of the 462 patients investigated, evidence of some cardiac abnormality was found in 150 (Table I). In slightly over half of those with cardiac involvement some associated heart disease was present, while in the remainder no cause for the disturbance other than thyrotoxicosis was apparent.

Comparison of Thyrotoxic Patients With and Without Cardiac Involvement

The importance of various factors in the development of cardiac complications was assessed by comparing the three groups of patients.

Age and sex distribution. The patients with cardiac involvement were in the older age groups (Fig. 1). This applied to patients both with and without associated heart disease (Fig. 2). Of 71 patients under 40 years of age treated with ^{131}I, 65 were in group I, two in group II, and four in group III. Women predominated in all the groups (Table II). There was no significant difference in the male:female ratio between patients with and without cardiac involvement. The increased incidence of women among patients with associated heart disease was largely attributable to the predominance of women with rheumatic valvular disease (10 out of 11 patients).

Presence of goitre. No difference was found between the different groups in the incidence of nodular goitre (Table III). Diffuse enlargement of the thyroid

was more commonly seen in patients without cardiac involvement, but these patients were also younger. No attempt has been made to separate a group based on the presence of a solitary adenoma, since frequently, on section, multiple nodules are found in a thyroid gland thought on palpation to contain only a single swelling (Mortensen, Woolner, and Bennett, 1955). No evidence was found, however, that nodularity of the gland, either single or multiple, was specially associated with the development of cardiac complications.

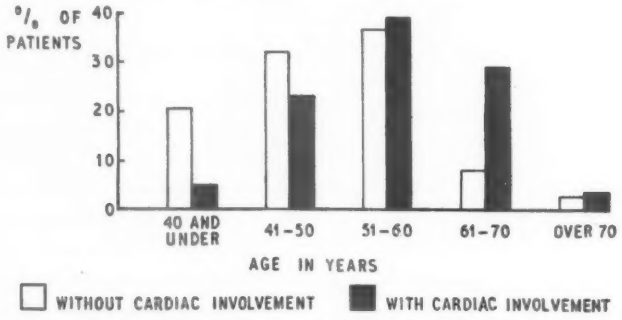

FIG. 1. Age distribution in 462 thyrotoxic patients with and without cardiac involvement.

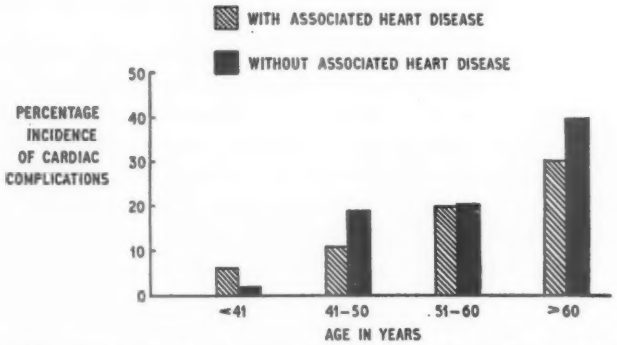

FIG. 2. Incidence of cardiac involvement in 462 thyrotoxic patients related to age.

Severity and duration of thyrotoxicosis. The mean four-hour uptake of ^{131}I on tracer study in the 64 patients of group III was 64·5 per cent.$\pm$1·9 (standard error). In 64 patients of group I of similar age and sex distribution the mean four-hour uptake was 64·1 per cent.$\pm$1·9 (standard error), no difference being apparent between these two groups. A similar comparison was carried out with respect to duration of thyrotoxicosis, the mean values$\pm$standard error being 34·2 months$\pm$4·9 in group III and 32·8 months$\pm$42·0 in group I, and again no significant difference was found.

Results of ^{131}I therapy of thyrotoxicosis. The results of therapy in the three groups were similar (Table IV). Nearly 60 per cent. became euthyroid after a single dose, usually within three months. The incidence of hypothyroidism was also similar. No exacerbations of hyperthyroidism or of cardiac disability were

observed in the few days after therapy, when acute destruction of the gland by the radiation was taking place. In the majority no specific antithyroid drug therapy was required after giving the ^{131}I, but in a few patients with severe cardiac disturbances a course of potassium iodide was given for about three weeks,

TABLE II

Sex Distribution of Patients

	Number	*Male:female ratio*
Group I. Thyrotoxic patients without cardiac involvement	312	1:4·0
Thyrotoxic patients with cardiac involvement	150	1:3·4
Group II. With associated heart disease	86	1:4·1
Group III. Without associated heart disease	64	1:2·8

TABLE III

Incidence of Goitre in 462 Thyrotoxic Patients With and Without Cardiac Involvement

	Number of patients	*Goitre absent*	*Nodular goitre*	*Diffuse goitre*
Group I. Without cardiac involvement	312	7·5%	43·4%	49·1%
With cardiac involvement:				
Group II. With associated heart disease	86	23·2%	44·2%	32·6%
Group III. Without associated heart disease	64	25·0%	40·6%	34·4%

TABLE IV

Results of ^{131}I Therapy in 462 Thyrotoxic Patients With and Without Cardiac Involvement

	Number of patients	*Euthyroid*			*Hypothyroid*	*Died before becoming euthyroid, untraced, or still hyperthyroid*
		1 dose	*2 doses*	*3 or more doses*		
Group I. Without cardiac involvement	312	60·6%	14·4%	5·1%	11·9%	8·0%
Groups II and III. With cardiac involvement	150	58·7%	16·0%	8·0%	9·3%	8·0%

beginning four or five days after the therapy dose. Even in patients not rendered euthyroid by a single dose of ^{131}I great reduction in thyroid activity followed the first dose, and a corresponding improvement occurred in the cardiac condition. The effect of the treatment of the hyperthyroidism on the cardiac disabilities is described subsequently.

Thyrotoxicosis and Associated Heart Disease

The thyrotoxic patients with various forms of associated heart disease (group II) have been studied particularly with regard to sex incidence and the presence of auricular fibrillation and congestive cardiac failure (Table V). The effect of

^{131}I therapy on these two cardiac complications is also shown but, as the numbers in some of the different sub-groups are small, these changes are mainly considered later as a whole in conjunction with the patients in group III.

Ischaemic heart disease. The diagnosis was based either on a typical history of angina pectoris or on electrocardiographic abnormalities. A large Q wave, indicating myocardial infarction or bundle branch block, in the absence of clinical evidence of any other pathological process affecting the conducting tissue, was taken as evidence of coronary artery disease. It was the commonest form of organic cardiac disease associated with thyrotoxicosis. The incidence

TABLE V

Group II: Patients with Associated Heart Disease

			Auricular fibrillation		*Congestive cardiac failure*			
					Prognosis after ^{131}I therapy			
	Total number	*Male*	*Female*	*Number*	*Spontaneous reversion after ^{131}I therapy*	*Number*	*Died from failure*	*Required mersalyl and/or digitalis*	*Complete relief*
Ischaemic heart disease	43	9	34	14	5	12	1	6	5
Angina pectoris	21	1	20	6	2	6	0	3	3
Myocardial infarction or ischaemia	22	8	14	8	3	6	1	3	2
Hypertension	22	3	19	9	5	9	2	4	3
Rheumatic heart disease	11	1	10	6	1	3	0	1	2
Pulmonary heart disease	8	4	4	5	2	4	3	0	1
Congenital heart disease	2	0	2	2	1	2	1	0	1

increased with age, and was greatest in the 61 to 70 years decade. Twenty-one patients gave a history of angina pectoris. They were slightly younger than the other patients with ischaemic heart disease, and women predominated, only one being a man. The majority were severely incapacitated by pain before the thyrotoxicosis was treated. After ^{131}I therapy, improvement occurred in 19 of the 21 patients. Ten were completely relieved of attacks of pain, and in the other nine some degree of relief was obtained. One patient failed to improve, and one became worse. In the remaining 22 patients there were gross electrocardiographic abnormalities, without angina pectoris, but in six there was a past history of myocardial infarction. Auricular fibrillation occurred in 33 per cent. of the patients with ischaemic heart disease, and there was spontaneous reversion to sinus rhythm in approximately one-third. Auricular fibrillation was present in nine of the 12 patients with congestive cardiac failure. The outcome of congestive cardiac failure was exceptionally favourable in this group (Table V).

Hypertension. In the present series hypertension has been arbitrarily defined as a diastolic pressure above 100 mm. recorded at any time before ^{131}I therapy. Twenty-two patients fell into this category; the high proportion of women is striking. Auricular fibrillation was present in 41 per cent. of these patients, and occurred in five out of the nine patients with congestive cardiac failure. The

possibility was considered that the conspicuous peripheral vasodilatation associated with thyrotoxicosis might reduce the blood-pressure in potentially hypertensive patients. The blood-pressure has accordingly been measured in patients actively hyperthyroid, and subsequently when they have become euthyroid. Patients with manifest hypertension, ischaemic heart disease, and uncomplicated cardiomegaly have been studied in this way, and have been compared with an equal number of patients of similar age and sex distribution from Group I (Table VI). All patients with auricular fibrillation have been excluded owing to

TABLE VI

Blood-Pressure Changes in 100 Thyrotoxic Patients after ^{131}I Therapy

	Number of patients	*Mean systolic pressure ±standard error (mm. Hg)*		*Mean diastolic pressure ±standard error (mm. Hg)*	
		Before ^{131}I therapy	*After ^{131}I therapy*	*Before ^{131}I therapy*	*After ^{131}I therapy*
Thyrotoxicosis without cardiac involvement (group I)	50	161·8 ±3·5	154·1 ±4·6	76·1 ±1·7	80·3 ±1·6
Ischaemic heart disease	25	169·4 ±3·4	176·0 ±1·4	83·6 ±6·5	90·2 ±3·1
Cardiomegaly alone	13	170·8 ±8·4	171·5 ±2·3	80·4 ±9·5	87·3 ±3·1
Hypertension	12	197·9 ±4·1	209·2 ±2·6	107·5 ±7·1	103·7 ±5·4

the difficulty in obtaining accurate blood-pressure readings. Only small, insignificant changes were observed after treatment, and there was no evidence that thyrotoxicosis masked the presence of hypertension as defined in this section. The blood-pressure readings in the patients with cardiomegaly alone are considered later.

Rheumatic heart disease. Seven of the 11 patients had mitral stenosis, and the remaining four had combined mitral and aortic valvular disease. Reversion to normal rhythm after successful treatment of the thyrotoxicosis occurred spontaneously in only one out of six patients, but was induced in another by the administration of quinidine.

Pulmonary heart disease. Seven patients had chronic bronchitis and emphysema, and one pneumonoconiosis. The equal sex distribution, and the high incidence of auricular fibrillation, and of death from congestive cardiac failure, are noteworthy.

Congenital heart disease. Two patients had congenital cardiac abnormalities and thyrotoxicosis. The first, a woman of 45 years, had auricular fibrillation and a patent ductus arteriosus, which became the site of a subacute bacterial infection. The latter was treated with penicillin, and the patient then had ^{131}I therapy. After successful treatment of the hyperthyroidism normal sinus rhythm developed spontaneously, but the congestive failure was not entirely relieved. This relief was finally achieved after ligation of the patent ductus. The

second patient, a woman of 58 years, had a patent interventricular septum, auricular fibrillation, and congestive cardiac failure. Some improvement followed ^{131}I therapy but, though the patient became euthyroid, the fibrillation persisted, and she died in congestive cardiac failure.

Cardiac Complications of Thyrotoxicosis

Sixty-four patients had auricular fibrillation, congestive cardiac failure, or cardiomegaly in the absence of any clinical, radiological, or electrocardiographic evidence of associated heart disease (Group III). This group is clearly of importance in attempting to determine the effect of hyperthyroidism on the heart, and the features associated with the development of these complications have accordingly been considered in detail.

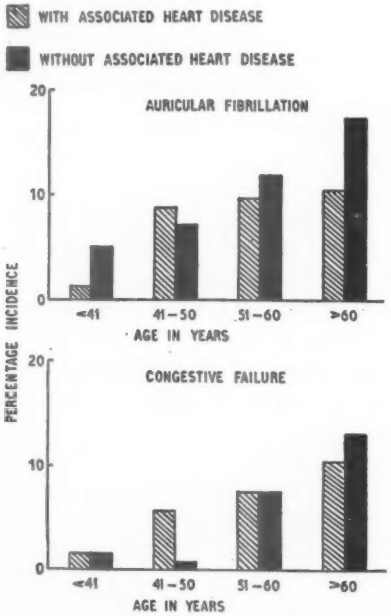

FIG. 3. Incidence of auricular fibrillation and congestive failure in 462 thyrotoxic patients related to age.

Auricular fibrillation was present in 75 per cent. of the patients in group III, but in only 42 per cent. of those in group II. The incidence increased progressively with advancing age when considered in relation to the 462 thyrotoxic patients in the study (Fig. 3). The prognosis in these patients after therapy is shown in Table VII. Over one-third of the patients in each group reverted spontaneously to sinus rhythm, the rate of reversion not differing significantly between the two groups. Quinidine was used for persistent fibrillation in only

14 patients; it was not given to the remaining patients with persistent fibrillation, because in them the condition was of long standing and associated with marked cardiomegaly. The rate of spontaneous reversion was higher in the younger age groups (Fig. 4), and also in male patients. In group III 53 per cent. of

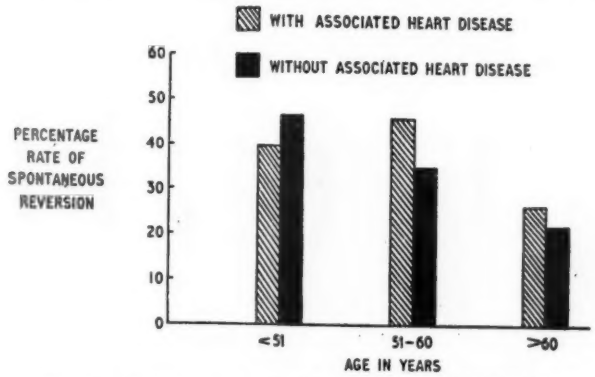

FIG. 4. Spontaneous reversion of auricular fibrillation after ^{131}I therapy related to age.

TABLE VII

Prognosis in 84 Patients with Auricular Fibrillation after ^{131}I Therapy

	Number of patients	*Reversion to sinus rhythm*	
		Number	%
Group II. With associated heart disease:			
Total with fibrillation	36	14	38·9
Male	7	3	42·9
Female	29	11	37·9
Quinidine treatment	2	1	50·0
Without congestive failure	15	10	66·7
With congestive failure	21	4	19·0
Group III. Without associated heart disease:			
Total with fibrillation	48	17	35·4
Male	17	9	52·9
Female	31	8	25·8
Quinidine treatment	12	4	33·3
Without congestive failure	25	11	44·0
With congestive failure	23	6	26·1

the male patients resumed sinus rhythm, but only 26 per cent. of the female patients, and this difference is significant ($P < 0{\cdot}05$). The presence of congestive cardiac failure adversely affected the rate of spontaneous reversion. In group II only 19 per cent. of the patients with failure reverted, compared with 67 per cent. without failure ($P < 0{\cdot}02$). In group III, fewer patients with congestive failure (26 per cent.) than without failure (44 per cent.) reverted spontaneously, but this difference does not attain statistical significance. Neither the type of goitre nor the severity or the duration of thyrotoxicosis bore any

significant relationship to the incidence of auricular fibrillation, or to the rate of spontaneous reversion.

Congestive cardiac failure occurred in 30 patients in group II (35 per cent.), of whom 28 were female and two male. In group III there were 26 patients with

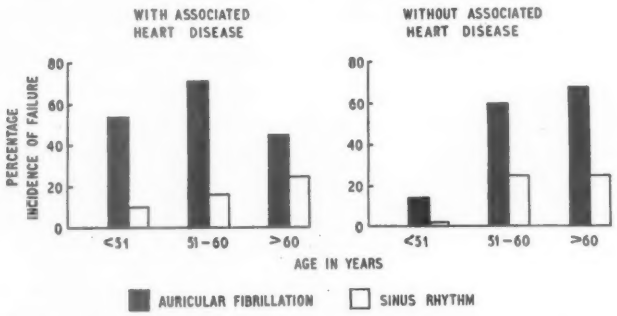

FIG. 5. Incidence of congestive failure related to incidence of auricular fibrillation in 150 patients with cardiac involvement (groups II and III).

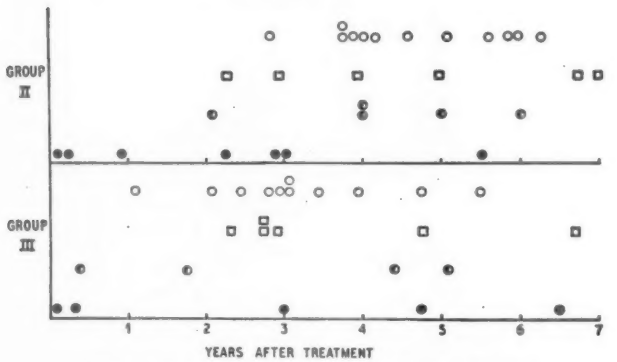

FIG. 6. Survival of individual patients in group II (with associated heart disease) and in group III (without associated heart disease) who had congestive cardiac failure before ^{131}I therapy.
● Died from congestive failure.
◐ Further attacks of failure after therapy.
□ No further attacks of failure, but maintained on digitalis, mersalyl, or both.
○ No further attacks of failure, and no auxiliary treatment required.

congestive failure (41 per cent.), comprising 21 women and five men. Congestive failure was seen more frequently in the older age groups (Fig. 3). The importance of auricular fibrillation in the development of congestive failure is shown in Fig. 5. In every age group the incidence of failure in patients with auricular fibrillation exceeded that in patients without auricular fibrillation. There was no significant relationship between the severity and duration of thyrotoxicosis and the production of congestive failure in either group. The

prognosis of the congestive failure is summarized in Table VIII. The survival and present condition of these patients in relation to time after ^{131}I therapy is shown in Fig. 6. The mortality rate from congestive failure is similar in both groups. In over half the patients in each group no further attacks of congestive failure have occurred after ^{131}I therapy, and over one-third in each group have required no further treatment with digitalis or mersalyl. An example of the relief of congestive cardiac failure that may result from ^{131}I therapy follows.

TABLE VIII

Prognosis of Congestive Cardiac Failure in 56 Thyrotoxic Patients Followed One to Seven Years after ^{131}I Therapy

	Group II With associated heart disease (30 patients)	*Group III Without associated heart disease (26 patients)*
Died from congestive failure	23·3%	19·2%
Further attacks of failure while on mersalyl and digitalis	16·7%	15·4%
No further attacks of failure while on mersalyl and/or digitalis	20·0%	23·1%
Relief of failure with treatment of thyrotoxicosis alone	40·0%	42·3%

Case 1. A housewife, aged 55 years, in July 1951 gave a history of increased sweating, nervousness, and loss of weight for nine months, and severe dyspnoea on exertion, with swelling of her legs and abdomen, for two months. On examination she had a nodular goitre, with a bruit over the gland, and obvious signs of thyrotoxicosis. She had auricular fibrillation, the apex rate being 150 per minute; the blood-pressure was 145/70, the heart was enlarged, the neck veins were markedly engorged, there was gross oedema of the legs and sacrum, the liver was enlarged, and ascites was present. X-rays of her chest showed gross cardiac enlargement and a right-sided pleural effusion. The ^{131}I tracer test confirmed hyperthyroidism (four-hour uptake 66 per cent., 48-hour protein-bound ^{131}I 3·8 per cent. per litre of plasma). A therapeutic dose of 12·2 mc of ^{131}I was then given, in August 1951, and treatment with digoxin and mersalyl maintained. Reassessment in October 1951 still showed evidence of thyrotoxicosis and signs of congestive failure, and a further dose of 17·7 mc of ^{131}I was given in November 1951. Treatment with digoxin and mersalyl was continued, and steady improvement occurred. She gradually lost all evidence of congestive failure, her apex rate fell to 80 per minute, and she was able to return to her housework. She was considered euthyroid in July 1952, and has been under regular observation up to April 1958, with no return of congestive failure. Treatment with digoxin, 0·25 mg. twice daily, has been maintained, as the fibrillation persisted, but she has required no further mersalyl since 1953. Chest X-rays taken in September 1956 showed persistence of cardiomegaly, but no pulmonary congestion or pleural effusion.

No significant relationship was present between the age or sex of patients and either mortality from congestive failure or relief of failure. Nor was there any correlation between the four-hour uptake of ^{131}I and the prognosis of congestive failure. The duration of thyrotoxicosis did not affect the mortality rate, but may possibly be important in relief of failure. Relief occurred in seven out of 12 patients who had had thyrotoxicosis for under one year, but 12 out of 14 patients

with thyrotoxicosis of over one years' duration had recurrent attacks of failure. This difference, however, does not attain statistical significance ($P > 0{\cdot}05$).

Reversion of auricular fibrillation to sinus rhythm greatly improved the prognosis of congestive cardiac failure. Considering groups II and III together, 29 of the patients with congestive cardiac failure had auricular fibrillation which persisted after ^{131}I therapy; eight of them died from congestive failure, and only two had complete relief of failure without ancillary measures. In contrast, there were eight patients with congestive failure who reverted to normal rhythm after ^{131}I therapy; all of them had complete relief, and there were no deaths. The following case is an example of long freedom from congestive failure following treatment with ^{131}I and the establishment of normal rhythm.

Case 2. A housewife, aged 56 years, gave a history of progressive breathlessness on exertion for six months, and ankle swelling, palpitations, and nervousness for six weeks. On examination she had raised jugular venous pressure, conspicuous ankle oedema, and auricular fibrillation with a pulse rate of 108; the blood-pressure was 100/75, and on clinical examination cardiac enlargement was present. There was no enlargement of the thyroid gland, but the patient appeared hyperkinetic, and had a fine tremor of her fingers and warm moist palms. The only other abnormal finding was an enlarged liver. Chest X-rays showed slight cardiac enlargement, and a ^{131}I tracer test confirmed hyperthyroidism (four-hour uptake 82 per cent., 48-hour protein-bound ^{131}I 1·28 per cent. per litre of plasma). She was treated with digoxin and given a therapeutic dose of 10 mc. of ^{131}I in October 1952. Treatment with digoxin, 0·25 mg. twice daily, was continued, and one month later she reverted spontaneously to sinus rhythm. During this period also she lost all evidence of congestive cardiac failure, and digoxin was stopped. She was considered euthyroid in December 1952, but in April 1953 she appeared hypothyroid, and treatment was begun with sodium L-thyroxine, 0·1 mg. daily. This dose was subsequently increased to 0·1 mg. twice daily in February 1954, and maintained at this level until the present time. She is fully active, and does all her own housework and shopping; her pulse has remained regular, and she has had no recurrence of congestive failure between November 1952 and April 1958.

Cardiomegaly. In 13 patients in the series of 150 with cardiac involvement cardiomegaly, proved radiologically, was present in the absence of auricular fibrillation, congestive cardiac failure, or associated heart disease. In five of these patients, in addition to postero-anterior chest X-rays, fluoroscopy was carried out to confirm enlargement of individual cardiac chambers before ^{131}I therapy, and in all 13 patients after therapy. In all 13 patients left ventricular enlargement was demonstrated by conspicuous increase in the transverse diameter of the heart in the postero-anterior view, and by the posterior cardiac border overriding the vertebral column in the left oblique view (Plate 26, Fig. 8 *a*, *b*). In addition, pulmonary artery enlargement was present in seven patients, and enlargement of the aortic arch in four. Four patients were 50 years of age or less, six were 51 to 60 years, and three were over 60 years. All were female. There was no difference in the duration and severity of the thyrotoxicosis between these patients and those with a normal heart size. The heart

size did not revert to normal in any patient after ^{131}I therapy. Electrocardiograms recorded in these 13 patients were compatible with the presence of left ventricular hypertrophy. In eight patients the sum of S in V1 and R in V5 or V6 (whichever is the larger) exceeded 35 mm., and thus satisfied the criteria laid down by Grubschmidt and Sokolow (1957) for the electrocardiographic diagnosis of left ventricular hypertrophy. In the other five patients the changes

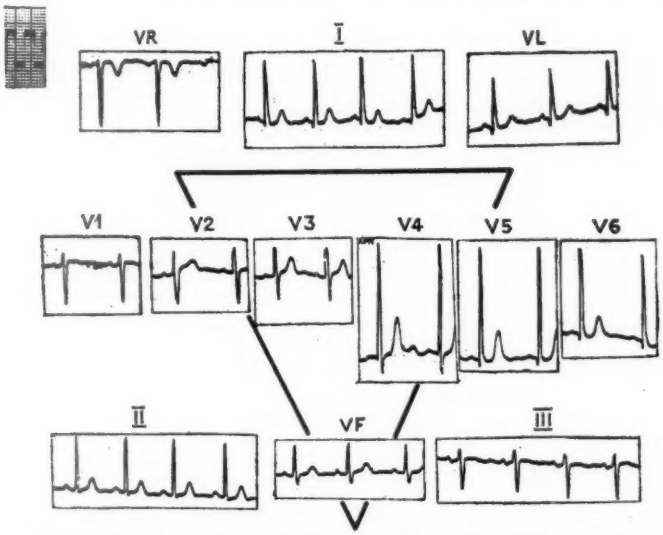

FIG. 7. Electrocardiogram of Case 3 showing left ventricular hypertrophy.

were not so great, but the tracings all showed left axis deviation and left ventricular predominance. After ^{131}I therapy the electrocardiographic evidence of left ventricular hypertrophy persisted unchanged, and no changes suggestive of myocardial ischaemia were seen at any time. In view of the clear evidence of left ventricular enlargement in these patients, the blood-pressure readings both before and after treatment have been studied in detail (Table VI). There was no gross elevation of either the systolic or diastolic pressure in these patients with cardiomegaly, and no significant changes followed ^{131}I therapy. Comparison, however, with the 50 patients in group I shows some interesting features. Before treatment there were no significant differences between the two sub-groups. Subsequently, when they were euthyroid, the patients with cardiomegaly showed both systolic and diastolic mean blood-pressure readings which were slightly but significantly higher than those found in the group I patients ($P < 0{\cdot}01$ for systolic and diastolic pressures). The case history of one of these patients with cardiomegaly follows as an example.

Case 3. A housewife, aged 47 years, gave a history of swelling in her neck for two years, and nervousness, excessive sweating, palpitations, lassitude, and loss of weight for eight months. There was no past history of acute rheumatism,

chorea, heart disease, or any serious illness. On examination she was hyperkinetic, with sweating palms, finger tremor, and a diffusely enlarged thyroid gland. Her pulse was regular at 84 per minute, the blood-pressure was 140/80, the heart was enlarged to the left, and a soft apical systolic murmur was heard.

TABLE IX

Post-Mortem Findings in Nine Thyrotoxic Patients with Cardiac Involvement

Case number	*Sex*	*Age (years)*	*Body weight at death (kg.)*	*Weight of heart (g.)*	*Clinical diagnosis*	*Summary of post-mortem findings*
Group II. With clinical evidence of associated heart disease:						
4	M	57	55·5	190	Pulmonary heart disease	Advanced vesicular emphysema. Hypertrophy of both ventricles. Mild coronary atheroma. Bicuspid aortic valve
5	M	70	54·3	..	Pulmonary heart disease	Diffuse vesicular emphysema. Hypertrophy of both ventricles
6	F	67	49·4	350	Hypertension	Hypertrophy of both ventricles. Slight fibrosis of mitral valve and chordae tendineae. Mild atheroma of coronary arteries and aorta
Group III. Without clinical evidence of associated heart disease:						
7	F	74	49·0	330	Thyrotoxic heart failure with auricular fibrillation	Hypertrophy of both ventricles. Marked atheroma of coronary arteries and aorta. Bronchopneumonia
8	F	80	47·8	..	Thyrotoxic heart failure with auricular fibrillation	Right ventricular hypertrophy; left ventricle normal. Suppurative pericarditis. Bilateral small pleural effusions. Coronary vessels healthy
9	F	37	52·3	500	Thyrotoxic heart failure with auricular fibrillation	Hypertrophy of both ventricles. Patchy myocardial fibrosis. Slight fibrosis of mitral valve. Coronary vessels showed minimal atheroma
10	F	61	52·3	200	Thyrotoxic heart failure with auricular fibrillation	Heart not enlarged. Coronary vessels healthy. Carcinoma of rectum with generalized metastases
11	M	52	40·8	380	Thyrotoxic heart failure with auricular fibrillation	Hypertrophy of both ventricles. Bilateral small pleural effusions. Coronary vessels healthy
12	F	66	42·8	390	Thyrotoxic heart failure with auricular fibrillation	Hypertrophy of both ventricles. Coronary vessels healthy. Bilateral pleural effusions

There was no evidence of heart failure. Chest X-rays showed left ventricular enlargement in both posterior-anterior and left oblique views (Plate 26, Fig. 8), the electrocardiogram indicated left ventricular hypertrophy (Fig. 7), and the ^{131}I tracer study confirmed thyrotoxicosis (four-hour uptake 80 per cent., 48-hour uptake 73 per cent., 48-hour protein-bound ^{131}I 1·72 per cent. per litre of plasma). She was given a therapeutic dose of 6·0 mc. of ^{131}I in November 1954, but required another dose of 5·6 mc. in August 1955, and became euthyroid in November 1955. She remained well from then up to April 1958, fully active and with no complaints; her blood-pressure was 140/85 at that time. The

cardiomegaly has persisted both on clinical and radiological examination, and there is still evidence of left ventricular hypertrophy on the electrocardiogram.

Autopsy findings. Post-mortem examinations were carried out in nine patients in the series. In three of these patients clear evidence of associated heart disease was present during life—cor pulmonale in two, and hypertension in one. The remaining six patients had auricular fibrillation and congestive cardiac failure during life, with no clinical evidence of associated heart disease on repeated examination. One of these six patients died from carcinoma of the rectum with generalized metastases, but the remaining five died from congestive cardiac failure. The post-mortem findings in these nine patients are shown in Table IX. The clinical diagnosis of cor pulmonale in two patients, and hypertension in one, was confirmed. No cardiovascular disease was found in the patient who died of carcinoma of the rectum, although during life congestive failure and auricular fibrillation had been present. In one of the remaining five patients conspicuous coronary atherosclerosis was present (Case 7). In one other patient (Case 9) there was slight coronary atheroma, not considered sufficient to produce the marked cardiac disturbance during life, especially as this patient was only 37 years of age when she died in heart failure. She was treated with ^{131}I, but refused to attend hospital for follow-up. It is probable that the hyperthyroidism was not fully controlled, but she was admitted to hospital moribund with pneumonia four months after the dose of ^{131}I. In the remaining three patients moderate to marked hypertrophy of one or both ventricles occurred, and no other possible aetiological factor producing heart disease, apart from thyrotoxicosis, was found. In these three patients also the coronary vessels were remarkably free of atheroma for their age. The myocardium was examined microscopically in these three cases, but no specific inflammatory or degenerative histological lesions were seen.

Discussion

The progressive increase in incidence of heart disease in thyrotoxicosis with advancing age, shown in the present series, is well recognized (Hurxthal, 1928; Ernstene, 1938; Griswold and Keating, 1949). The age distribution was similar in patients with and without evidence of associated heart disease. The female: male ratio in patients with cardiac involvement, 3·4:1 in the whole group, was close to that found in the thyrotoxic patients without cardiac complications, 4·0:1. This result contrasts with the findings of Friedberg (1950), who reported a female:male ratio of 5:1 in thyrotoxicosis without heart disease, and of 2:1 when heart disease was also present. Friedberg's sex ratio in thyrotoxic patients without heart disease refers, however, to thyrotoxicosis at all ages, but in the present series the patients with and without heart disease were of comparable ages, since patients under 40 years have seldom been treated with ^{131}I. Diffuse goitre predominated in younger patients without heart disease, but nodular goitre was not particularly associated with the development of cardiac complications.

McPhedran (1942) and Maher and Sittler (1936) found an increased incidence of nodular goitre in thyrotoxic patients with heart disease, but Griswold and Keating (1949) reported an equal incidence of nodular and diffuse goitre. Neither duration of thyrotoxicosis nor severity of thyrotoxicosis (assessed with the help of ^{131}I tracer study) appeared to be relevant factors in producing cardiac complications in the 64 patients with cardiac involvement but with no evidence of associated heart disease. These findings are unlike those of Andrus (1929), who suggested that cardiac complications were related to intensity of thyrotoxicosis, and those of Griswold and Keating (1949) and Ernstene (1938), who considered that duration of thyrotoxicosis was important. These conclusions were not supported by a statistical analysis of the results. Hurxthal (1928), however, did not find any relationship between these two factors and the incidence of cardiac complications.

The incidence of auricular fibrillation increased with age, both in patients with and in those without associated heart disease; a similar finding was reported by Ernstene (1938). In 48 patients with auricular fibrillation no clinical evidence of associated heart disease could be found; Maher and Sittler (1936), on the other hand, found that auricular fibrillation in thyrotoxicosis was almost invariably associated with coexistent organic heart disease. There was a relative increase in the number of men with auricular fibrillation when associated heart disease was absent; Lerman and Means (1932) reported a similar increased incidence of auricular fibrillation in male patients, the majority of whom had no associated heart disease. There was no significant difference in incidence of goitre among patients with auricular fibrillation. Willius, Boothby, and Wilson (1923), Lahey (1929), and Griswold and Keating (1949) found a similar equal dispersion of goitre type, but Magee and Smith (1935) reported an increased incidence of auricular fibrillation in adenomatous goitre, attributing it to the increased age of patients with this type of goitre. Willius, Boothby, and Wilson (1923) and Ernstene (1938) found that longer duration of thyrotoxicosis is more prone to produce auricular fibrillation, but this finding was not confirmed in the present series. Auricular fibrillation is unusual in chronic pulmonary heart disease (Wood, 1956; Oswald, 1958). Stuart-Harris and Hanley (1957) found it in only three patients out of 110, and in two of these it was transient. Auricular fibrillation was found in five out of eight patients with chronic pulmonary heart disease in the present series, this high incidence being attributable to the presence of coexistent hyperthyroidism. The rate of spontaneous reversion to normal rhythm after ^{131}I therapy in the present series, approximately just over one-third of the cases of auricular fibrillation, was lower than that usually described after partial thyroidectomy. Griswold and Keating (1949) and Anderson (1932) reported a post-operative reversion rate of approximately 50 per cent., but the reduced rate in the present series is probably a reflection of the increased severity of cardiac involvement. A similar low rate of post-operative reversion, 33 per cent., was reported by Ernstene (1938), and an even lower rate, 20 per cent., by Rosenblum and Levine (1933).

The incidence of congestive cardiac failure increased with age, and this

tendency was also found by Hurxthal (1928), Andrus (1932), and Likoff and Levine (1943). There was a predominance of female patients with failure, most marked when associated heart disease was present; Likoff and Levine (1943) and Griswold and Keating (1949) found a similar predominance of women among thyrotoxic patients with congestive failure. Auricular fibrillation was the most important factor in producing congestive failure in the present series, and this has been confirmed by other authors (Hurxthal, 1928; Ernstene, 1938; Likoff and Levine, 1943). Duration of thyrotoxicosis did not appear to be an important factor in producing congestive failure, as has been claimed by Andrus (1932), Griswold and Keating (1949), and Friedberg (1950). Intensity of toxicity was also regarded as important by Hurxthal (1928) and Andrus (1929), but this view was not confirmed in the present series. The prognosis of congestive failure after treatment was favourable in view of the age of the patients and the severity of the cardiac complications. More than half of the patients had no recurrence of congestive failure during a follow-up period of one to seven years, and the majority of these patients required no further treatment with digitalis or mersalyl. Likoff and Levine (1943) reported 21 patients with congestive failure and thyrotoxicosis, but with no evidence of associated heart disease, whose condition was followed for five to 10 years after thyroidectomy, and in no patient was there a recurrence of failure. Lahey (1934) reviewed 303 thyrotoxic patients with cardiac involvement, of whom 216 had congestive cardiac failure, and found that, of 208 living patients, only 1·5 per cent. were still completely incapacitated five years after thyroidectomy. Forty-eight had died, but in most cases from non-cardiac causes.

The radiological appearance of the heart in thyrotoxicosis, in the absence of auricular fibrillation, congestive failure, or associated heart disease, has been described by Parkinson and Cookson (1931). Generalized cardiac enlargement is the usual finding, and may be preceded by enlargement of the pulmonary artery. Dilatation of the aorta is rather less frequent. The 13 patients in the present series with cardiomegaly alone showed left ventricular enlargement only, and not generalized enlargement, but dilatation of the pulmonary artery and of the aortic arch was common. The incidence of uncomplicated cardiomegaly was not related to increase of age, as described by Coller (1924) and Hurxthal (1930). The presence of cardiac hypertrophy in thyrotoxicosis, in the absence of auricular fibrillation, congestive failure, or associated heart disease, has been described by a number of observers (Smith and Colvin, 1927; Hurxthal, 1928). Friedberg and Sohval (1937) studied the occurrence and pathogenesis of cardiac hypertrophy in 27 fatal cases of thyrotoxicosis, and concluded that hypertrophy was absent in uncomplicated cases with no associated heart disease. It has been suggested that cardiomegaly in thyrotoxicosis may be due to the presence of an arteriovenous aneurysm, either in the thyroid (Boas, 1923) or generalized, associated with widespread peripheral vasodilatation. A frequent feature of cardiomegaly associated with arteriovenous aneurysm is its reversibility when the aneurysm has been treated, provided no primary cardiac disease is present (Hoover and Beams, 1923). On the other hand, if a large arteriovenous aneurysm has been

present, the increased cardiac output does not fall to normal levels on closure of the shunt (Cohen, Edholm, Howarth, McMichael, and Sharpey-Schafer, 1949). In our 13 patients there was both radiological and electrocardiographic evidence of left ventricular enlargement, and a return to normal was not seen after ^{131}I therapy. Where, however, there is electrocardiographic evidence of left ventricular hypertrophy, but no radiological evidence of enlargement, a return of the electrocardiogram to normal may occur after ^{131}I therapy (Sandler, 1959). Cardiac enlargement produced by thyroxine in animals is reversible (Hewitt, 1920). The presence of both radiological and electrocardiographic changes apparently represents a more severe and permanent form of cardiac damage, whereas electrocardiographic abnormalities alone may constitute an earlier stage, which is still reversible. The cause of the cardiac enlargement in these 13 patients is not clear. When they were compared with thyrotoxic patients free from cardiac complications, the only difference found was a slight increase in both systolic and diastolic blood-pressures, which was detectable only when they had become euthyroid. The levels of blood-pressure in these patients with cardiomegaly, however, would in normal circumstances scarcely be considered a sufficient explanation of the observed degree of left ventricular enlargement, though this small extra load on the thyrotoxic heart may be a contributory factor.

The association of angina pectoris and thyrotoxicosis has been regarded as uncommon. Haines and Kepler (1930) described 33 cases, Lev and Hamburger (1932) six cases, Rosenblum and Levine (1933) nine cases, and Somerville and Levine (1950) 24 cases. In the present series ischaemic heart disease was present in 43 patients, and 21 of these had angina pectoris. The incidence of myocardial ischaemia increased with age, and the female:male ratio in our series was approximately 4:1, unlike angina pectoris without thyrotoxicosis, where the ratio is usually 1:3 or 4 (White, Bland, and Miskall, 1943). Somerville and Levine (1950) found the sex ratio similar to that of angina without thyrotoxicosis, Haines and Kepler (1930) found an approximate 1:1 ratio, and Lev and Hamburger (1932) a ratio of 2:1. No significant difference in incidence of goitre was present; in this our findings were unlike those of Maher and Sittler (1936), who reported a significant increase of toxic adenoma. Lev and Hamburger (1932) reported a two-thirds improvement rate in angina in hyperthyroid patients after thyroidectomy. Somerville and Levine (1950) found improvement in 13 out of 15 patients after thyroidectomy, and in four out of five patients after a course of thiouracil. Improvement occurred in 20 out of the 21 patients in our series after treatment with ^{131}I.

There has been considerable controversy as to whether thyrotoxicosis alone can cause heart disease, in the absence of any associated condition such as coronary artery disease, hypertension, or rheumatic or other heart disease. Willius, Boothby, and Wilson (1923) in a study of 377 thyrotoxic patients, concluded that cardiac disease was infrequent, not more than 2 per cent. of patients having sufficient clinical evidence of myocardial injury to suggest serious heart disease. Similar views were held by Lahey and Hamilton (1924), who stated

that 'young individuals with previously undamaged hearts suffer no cardiac changes, no matter how intense the hyperthyroidism'. Hurxthal (1928), in a study of 500 cases of thyrotoxicosis, claimed that there was no evidence that thyrotoxicosis injures normal healthy hearts, because there was very little, if any, evidence of cardiac damage in patients under 40 years of age; nine of his patients had congestive cardiac failure, but, as they were in the older age groups, he assumed that there was underlying heart disease. The belief that thyrotoxicosis can cause cardiac damage is, however, held by other authors. Griswold and Keating (1949) found 18 out of 54 thyrotoxic patients with congestive cardiac failure in whom no clinical evidence of primary associated heart disease could be found. Likoff and Levine (1943) reported 21 patients with congestive failure among 409 thyrotoxic patients, and no discoverable cause for the failure other than thyrotoxicosis; furthermore, after subtotal thyroidectomy all 21 patients recovered from failure, and no recurrence was observed in a five- to ten-year follow-up period. Magee and Smith (1935) found 35 out of 200 thyrotoxic patients with auricular fibrillation in whom no clinical evidence of pre-existing cardiac disease was present, and also 29 out of 62 patients with congestive failure in whom hyperthyroidism was the only cause found for the failure. In the present series of 150 patients, 64 had cardiac involvement in the absence of any clinical evidence of associated heart disease on repeated examination. Twenty-one of these patients had congestive cardiac failure; 13 had no recurrence of failure after treatment with ^{131}I, and five of these required no further treatment with digitalis or mersalyl. Furthermore, post-mortem examination in five of these patients with congestive failure, but without clinical evidence of associated heart disease during life, did not reveal any other possible factor producing heart disease in four cases. Kepler and Barnes (1932) also found, on post-mortem examination of 27 thyrotoxic patients with congestive failure, nine in whom no cause for the failure other than hyperthyroidism could be detected.

A difference of opinion also exists as to the histopathological effects of hyperthyroidism on the heart. Fahr (1916) found focal necrosis and interstitial myocarditis in five fatal cases of thyrotoxicosis. Hashimoto (1921) found similar changes in two further cases. Wilson (1923), from a study of 18 cases, concluded that 'in patients with long-sustained pronounced hyperthyroidism, the myocardium shows more advanced fat changes than in individuals of the same age without hyperthyroidism'. Specific myocardial lesions have also been found by Goodall and Rogers (1927) and Lewis (1932). On the other hand, Goodpasture (1921) found myocardial necrosis in two fatal cases of auricular fibrillation and thyrotoxicosis, but conditions other than thyrotoxicosis were also present, and might have accounted for the lesions. Rake and McEachern (1932) reported similar results, and found no relationship between clinical manifestations of hyperthyroidism and structural changes in the heart in 27 autopsies. Weller, Wanstrom, Gordon, and Bugher (1932) drew very similar conclusions from 35 fatal cases. The heart was examined histologically in three patients in our series who died from congestive failure, and in whom there was no clinical or

post-mortem evidence of associated heart disease, but no specific myocardial lesions were found.

Control of thyrotoxicosis in patients with severe heart disease may be attained in one of three ways: radical surgery, antithyroid drugs, or ^{131}I. Lahey (1930) maintained that there are practically no cases of thyrotoxicosis with cardiac decompensation which are not amenable to surgery, but Hurxthal (1940) found an eight times greater mortality after thyroidectomy in thyrotoxic patients with congestive failure or uncontrolled auricular fibrillation than in patients with uncomplicated thyrotoxicosis. Gross congestive failure, especially if incompletely controlled before operation, is associated with a poor operative risk. Antithyroid drugs are often useful in such patients, but are an unsatisfactory form of long-term treatment. When severe cardiac complications are present it is necessary to obtain complete and permanent control of the thyrotoxic state. Radioactive iodine is the treatment of choice in many of these patients with severe heart failure. They are of the accepted age group, and it can be administered to any patient, no matter how severely ill or bedridden he may be. Complete control of the hyperthyroidism is attained in nearly two-thirds of the patients with one dose, and within one to three months. Even in patients requiring more than one dose great improvement has invariably followed the first treatment. The hazard of carcinoma of the thyroid after exposure to ionizing radiations must be considered. No case of thyroid carcinoma following ^{131}I treatment of thyrotoxicosis has been recorded in published reports, and it has been widely used during the last 10 years. It is generally accepted that the latent period for development of carcinoma after ionizing radiation in adult life is 20 to 30 years (Medical Research Council, 1956); this, therefore, does not constitute an important risk in such middle-aged patients with severe heart disease. The incidence of myxoedema following surgery is inversely proportional to the incidence of recurrent hyperthyroidism (Crile and McCullagh, 1951). Although conservative thyroidectomy may produce a lower myxoedema rate than that obtained with ^{131}I, the increased risk of recurrence of toxicity, with serious or even fatal relapse of heart disease, is always present. The myxoedema rate in the present series was just over 9 per cent. in the patients with heart disease, and there is no doubt that such patients fare better from the cardiac point of view when slightly hypothyroid.

On reviewing the evidence provided by the clinical investigation, response to treatment with ^{131}I, and autopsy findings, in our own cases and accumulated from the experience of previous authors, some tentative opinions and conclusions may be expressed. There is no doubt that the incidence of all the cardiac complications of thyrotoxicosis increases with advancing age, and thus runs parallel with the appearance of hypertensive cardiovascular disease and coronary atherosclerosis. In the older age groups some degree of coronary atheroma is almost invariably present, and the blood-pressure shows a slow progressive increase (Hamilton, Pickering, Roberts, and Sowry, 1954). Nevertheless, in our own series severe cardiac complications have appeared in patients without undue hypertension, and with remarkably healthy coronary arteries.

Experimentally, cardiac enlargement is readily produced by the administration of thyroid extract (Hashimoto, 1921), and we have recently confirmed and extended these observations by giving thyroxine to rats (Sandler and Wilson, unpublished). There is thus considerable evidence to suggest that hyperthyroidism is often the major factor in the production of cardiac complications, though the precise mechanism for the increased susceptibility of the human heart with advancing age remains uncertain. Further support for this view comes from a comparison of the patients falling into our groups II and III. In a few cases, where there has been coexistent severe hypertension, coronary artery disease, or pulmonary disease, the residual disability after treatment of the thyrotoxicosis has been considerable. The outstanding feature, however, in the majority of patients is the large measure of improvement in the cardiac condition that results from suppression of the hyperthyroidism, whether or not there is evidence of some associated cardiac disease. This is particularly noticeable in the almost equal rates of reversion of auricular fibrillation to normal rhythm, and in the similar prognosis of cardiac failure, in the two groups. Clearly all degrees of degenerative heart disease may be associated with hyperthyroidism, but severe cardiac complications may develop even in the presence of only minimal atheroma. Whatever the association may be, treatment of the thyrotoxic element is of vital importance. The administration of a therapeutic dose of ^{131}I carries no immediate risks, and is an ideal form of therapy for thyrocardiac patients.

We should like to thank many past and present members of this Department, and of the Sheffield National Centre for Radiotherapy, who have assisted in the care of our patients; the physicians and surgeons of the United Sheffield Hospitals and Sheffield Regional Hospital Board, who have referred patients for treatment; the pathologists who kindly allowed us access to their reports and material; and Dr. J. Wilkie and the staff of the Radiology Department, Sheffield Royal Infirmary, for their helpful co-operation.

Summary

1. Evidence of heart disease was present in 150 out of 462 thyrotoxic patients treated with radioactive iodine at Sheffield between 1949 and 1956. Eighty-six of these patients had associated heart disease, comprising ischaemic, hypertensive, rheumatic, pulmonary, and congenital heart disease. The remaining 64 patients had auricular fibrillation, congestive cardiac failure, or cardiomegaly alone, in the absence of any clinical, radiological, or electrocardiographic evidence of associated heart disease.

2. Thyrotoxic patients with cardiac involvement were found in the older age groups. Sex, incidence of goitre, and severity and duration of thyrotoxicosis did not appear to be related to the incidence of cardiac involvement.

3. Approximately one-third of the patients with auricular fibrillation reverted spontaneously to normal rhythm after ^{131}I therapy, the most important factor

adversely influencing reversion being the presence of congestive failure. The rate of reversion was higher in younger patients and male patients.

4. More than half of the patients with congestive cardiac failure had no further attacks of failure after ^{131}I therapy, and more than one-third required no further treatment with digitalis or mersalyl. The prognosis in patients with congestive failure and auricular fibrillation was more favourable if sinus rhythm was restored.

5. In 13 patients without associated heart disease there was radiological and electrocardiographic evidence of left ventricular enlargement in the absence of auricular fibrillation and congestive cardiac failure. A return to normal did not occur after ^{131}I therapy.

6. Post-mortem findings in nine patients in the series are discussed. In four of these cases no cause of heart failure other than thyrotoxicosis was found.

7. The role of thyrotoxicosis alone in causing heart disease, and the importance of undetected coronary artery disease and masked hypertension, are considered. It is concluded that although thyrotoxicosis may not be the sole cause of the cardiac disability, in many patients with thyrotoxicosis and heart disease it is nevertheless the predominant factor.

8. ^{131}I therapy is safe and effective, and is the treatment of choice in thyrotoxic patients with severe cardiac complications.

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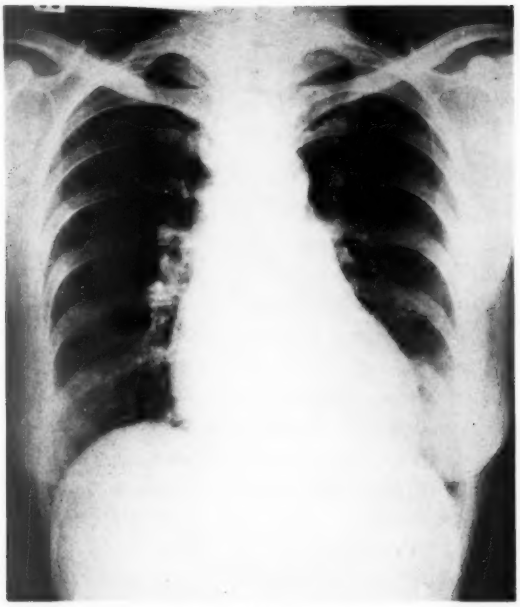

(*a*)

(*b*)

FIG. 8. Postero-anterior (*a*) and left oblique (*b*) views of Case 3 showing cardiomegaly and left ventricular enlargement

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THE EARLY DIAGNOSIS OF THE CAUSES OF HAEMATEMESIS[1]

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In spite of advancing knowledge in the fields of diagnosis and pathology, there is evidence that peptic ulcer and its complications, and particularly gastro-intestinal bleeding, are becoming more rather than less frequent. Estimates of the clinical incidence of this complication of peptic ulcer vary from one-quarter (Crohn, 1950) to approximately one-third of all patients (Hurst and Ryle, 1937). An authoritative source (*British Medical Journal*, 1950) estimated that between 20,000 and 30,000 patients are admitted annually to hospitals in England and Wales owing to gastroduodenal haemorrhage, and that nearly half the 5,000 deaths each year from peptic ulcer may be the result of this complication.

Diagnosis of the Causes of Haematemesis

Despite extensive writings on the causes and proper management of haematemesis, the initial diagnostic difficulties encountered in this common medical emergency become lost in tables of final diagnosis. Most reports recognize the difficulty experienced during the acute stages of haemorrhage in identifying the cause. Peptic ulcer is undoubtedly the most important cause of the admission of patients for haematemesis and melaena. Of Jones's series (1956) of 1,910 admissions for this emergency, 1,764 were due to proved or probable peptic ulcer. Fraenkel and Truelove (1956) reviewed 845 cases of haematemesis among hospital patients. Seven out of every 10 showed convincing evidence of chronic peptic ulcer; acute ulcers accounted for haematemesis in a further one in every six patients. The only other single causes, in both series, which contributed appreciable numbers were oesophageal varices and carcinoma of the stomach. In the United States, however, portal hypertension from cirrhosis caused haematemesis in 12·5 per cent. of patients reported by Schiff and Shapiro (1951). Though in most patients with chronic ulcers radiological or operative confirmation is obtained, this is rarely so in the case of bleeding acute ulcers. Thus Needham and McConachie (1950) could give only an approximate estimate of the proportion of their patients with haematemesis who had bled from acute peptic ulcer. Jones (1956) and Tanner (1954) achieved greater diagnostic accuracy by early gastroscopy combined with surgery and radiology, judging between 6·5 per cent. and 29·3 per cent. to have bled from acute ulcers. In most

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series this diagnosis rests upon negative radiological findings. While a short history of preceding dyspepsia is more commonly found in patients bleeding from acute than from chronic peptic ulcer, this is not invariably so. If chronic ulcer lesions could be confidently identified, and earlier surgery undertaken, the mortality from haematemesis could be reduced from its present unsatisfactory level. As early as 1918 Finsterer proposed operation 24 to 48 hours from the onset of haemorrhage; the mortality in his early cases was 5 per cent. (Finsterer, 1939). Gordon-Taylor (1935) commented: 'Finsterer's first 48 hours is still the optimum period for surgical attack in haematemesis'; and Tanner (1954) found that best results were obtained by early and frequent surgery. While the mortality with medical management can be as low as that achieved by Meulengracht (1935), it is unlikely that a universal surgical approach will provide comparable success and achieve wide popularity. To a large extent treatment must be determined by the facilities available. In general, surgical intervention has been limited to selected patients (Bohn, 1949; Parsons and Aldridge, 1951; Pedersen, 1951), the best results being obtained by prompt surgery in patients with proved or probable peptic ulcers. As Tanner (1950) has stressed, the criterion for success or failure of a surgical policy is its influence on overall mortality, and not the mortality for surgical intervention as such, which depends on the type of risk accepted. Jones (1952) showed that in middle-aged or older subjects with chronic peptic ulceration the mortality is high with medical treatment, and that it is in such patients that the best surgical contribution to the reduction of mortality can be achieved, provided an early decision is made in suitable cases.

Acute peptic ulceration is a common lesion which normally responds well to medical treatment, but a firm distinction between acute and chronic ulcer is impossible on clinical grounds alone. With mounting recognition of the role of surgery in the treatment of bleeding chronic ulcer, and of the good prognosis of the bleeding acute lesion with medical management, the inadequacy of present diagnostic methods assumes increasing importance. Early barium-meal examination has been adopted in some centres as a means of obtaining more precise information. The technique elaborated by Hampton (1937) and followed by Schatzki (1946), though considered safe by many observers, is not without risk of initiating haemorrhage, and such examinations are frequently unsatisfactory. Early gastroscopic examination is a feasible undertaking in most patients, and is of positive value if the lesion responsible for bleeding lies in the stomach. Determination of urinary pepsinogens, as reported by Janowitz, Levy, and Hollander (1950), may also aid early diagnosis. Liver-function studies (particularly the bromsulphthalein retention test) aid in the recognition of bleeding oesophageal varices consequent upon cirrhosis. Decisions as to treatment most often depend on clinical judgement, and there is need for a safe bedside method that will yield reliable diagnostic and prognostic information.

Gastric Intubation in Haematemesis

Kaufman (1910) and Hurst (1924) recommended gastric lavage in the acute stages of haematemesis, to empty the distended stomach and thereby to secure

its contraction and arrest haemorrhage, but criticism was directed chiefly to the potential danger of an indwelling tube irritating the gastric mucous membrane and initiating further bleeding. Soper (1931) treated haematemesis by continuous aspiration of stomach contents for three days, and found the method of use both in the detection of recurrent bleeding and as an aid to ulcer healing. Wangensteen (1940), Kinsella (1950), and Lewis (1950) also reported favourably on the value of gastric aspiration in haematemesis. Chandler and Watkinson (1953), in a study of 105 patients with gastroduodenal haemorrhage, found that the bedside observation of blood-staining in gastric samples aspirated at hourly intervals was of value in the treatment of individual patients; early warning of further haemorrhage was often obtained, and occasionally information about the site of the bleeding was provided. More recently Dawson (1956) concluded that the method offered no real advantage over other clinical criteria in the prediction of recurrent bleeding.

Measurement of Gastric Acidity in Gastrointestinal Bleeding

No previous experimental observations of the effects of gastrointestinal bleeding on gastric secretion have been made. On the assumption that secretory changes of diagnostic importance might accompany bleeding, it became necessary to appraise methods used in the assessment of gastric acidity, to determine which might be most appropriate. The fractional test meal devised by Rehfuss (1914) and Bennett and Ryle (1921) gives only a fragmentary impression of changes in acid secretion and has many inadequacies, and admixture with blood makes titration of the gastric contents difficult. Continuous aspiration techniques (Sandweiss, Friedman, Sugarman, and Podolsky, 1946; Levin, Kirsner, Palmer, and Butler, 1948), and studies of basal secretion (Bloomfield, Chen, and French, 1940; Berk, Rehfuss, and Thomas, 1942), require prolonged fasting, and would be invalidated by blood-staining. Serial test meals (Hunt, 1951) and the augmented histamine test (Kay, 1953) are probably the most reliable measurements of gastric acidity, but require repeated observations or the administration of large doses of histamine, and share the disadvantage of requiring a fasting patient.

Acidity can be measured by titration or by determination of pH. Titration raises difficulties in respect of the indicator used to determine end-point, and Shay, Komarov, and Berk (1950) have questioned the necessity of using Töpfer's reagent, particularly to indicate the presence of achlorhydria. Berk, Thomas, and Rehfuss (1942) noted that variable interpretation of end-points with Töpfer's reagent and with phenolphthalein may lead to significant errors in the assessment of acidity of aspirated gastric samples. Electrical pH determination is both accurate and convenient, and is unaffected by the presence of blood or food in the stomach. James and Pickering (1949) showed that the theoretical relation between pH and hydrogen ion concentration in aqueous solutions of hydrochloric acid applied, with reasonably close agreement, to gastric samples.

The inadequacies of previous methods led James and Pickering (1949) to

devise 24-hour gastric analysis, whereby changes of intragastric acidity under normal dietary conditions were observed by sampling gastric contents hourly and estimating pH electrometrically. In duodenal ulcer the curves of intragastric acidity differed from normal in showing a generally higher level of acidity, a less conspicuous neutralization after food, and the maintenance of higher acidity at night after food had disappeared from the stomach. In most patients with gastric ulcer a nocturnal reduction in acidity occurred, approximating to alkaline levels. Watkinson (1959) used the same method to investigate changes of pH of the gastric contents in 405 subjects, of whom 44 were normal controls and 286 were ulcer patients. Mean pH values in normal subjects varied between 2·0 and 3·55, neutralizing effects of meals were apparent, and levels of nocturnal acidity were low. One hundred and twenty-two duodenal ulcer subjects maintained more acid intragastric pH values throughout the 24 hours, particularly in post-prandial periods through the day and at most hours during the night. One hundred and twenty-eight patients with gastric ulcer showed values significantly less acid than normal, sporadically through the day and in most of the night specimens. Comparison of mean hourly pH values showed highly significant differences between gastric and duodenal ulcer at all hours. Dominant secretion patterns were found in all groups; 72·7 per cent. of control subjects showed normal night acidity, 67·2 per cent. of duodenal ulcer patients had high night acidity, and somewhat less than half (42·4 per cent.) of gastric ulcer subjects showed nocturnal neutralization. Using 24-hour gastric analysis, Watkinson and James (1951) studied 22 patients who had shown a histamine-fast achlorhydria on one or more occasions; in 12 the achlorhydria was associated with peptic ulceration. Their results cast doubt on the reliability of histamine test meals in the diagnosis of achlorhydria, for in 10 of the 12 pH values below 3·0 were recorded for periods varying between four and 18 hours. These results again stressed the fact that normal food is as effective as histamine in the stimulation of acid secretion. The evidence indicated that the Rehfuss histamine meal overestimates the incidence of achlorhydria, especially in cases associated with peptic ulcer.

The results obtained by the use of 24-hour gastric analysis in the study of uncomplicated peptic ulcer suggested its application during the acute stages of gastroduodenal haemorrhage. It was thought that two purposes might be served by such a study: first, that some abnormality of secretion of diagnostic value might be present; and secondly, the use of an indwelling tube seemed to offer theoretical advantages in the management of patients suffering from haematemesis, which required practical trial. These assumptions had been justified by early experience (Chandler and Watkinson, 1953).

Analysis of Clinical Cases

Two hundred and thirty-eight patients, admitted urgently with haematemesis or melaena, or both, to the General Infirmary at Leeds, and to St. James's Hospital, Leeds, were studied by means of an indwelling gastric tube and 24-hour

gastric analysis. They represented consecutive and unselected admissions for gastroduodenal bleeding over the period 1953 to 1955 inclusive. The difficulty experienced in identifying the site of bleeding in haematemesis is well recognized, since in the acute stages there is no certain method of diagnosis save operation, and the final conclusion must often be reached in retrospect. Even at necropsy it may be impossible to decide the source of bleeding, especially if multiple lesions exist. The assumed cause of bleeding, and the criteria employed in diagnosis, are summarized in Table I.

TABLE I

Patients Investigated

		Diagnostic Criteria				
			Radiography			
Diagnosis	*Number of cases*	*Operation*	*Positive*	*Negative*	*Gastro-scopy*	*Necropsy*
Chronic gastric ulcer	40	15	25	..	6	1
Chronic duodenal ulcer	76	15	67	..	..	5
Acute ulcer	96	9	3	77	24	5
Post-operative	10	4	5	..	6	..
Hiatus hernia	7	..	7	..	..	..
Carcinoma of stomach	4	4	2	..	..	..
Portal hypertension	1	1	1	..	..	..
Miscellaneous	4	..	..	..	..	..
Total	238	48	110	77	36	11

In many patients the investigations were duplicated.

Chronic gastric ulcer. The ulcers in the 40 patients in this group were shown at operation in 15, by radiological examination in 25, by gastroscopy in six, and at necropsy in one case. All ulcers were considered benign; they were associated with duodenal ulcer in two cases, pyloric stenosis in one, oesophageal hiatus hernia in one, and chronic myeloid leukaemia in one case. Pulmonary tuberculosis and angina contributed to death in the fatal case.

Chronic duodenal ulcer. In the 76 patients so classified, the ulcer was demonstrated at operation in 15, radiologically in 67, and at necropsy in five cases. Associated lesions were oesophageal hiatus hernia (three cases), pyloric stenosis (one), chronic nephritis (one), Paget's disease (one), and previous coronary thrombosis (one case). There were five deaths: one patient died on the fifth day in hospital from coronary thrombosis, necropsy revealing, in addition, wide dissemination of carcinoma from a primary growth in the lung; a second died one year later from congestive heart failure secondary to calcific aortic stenosis; and three died in the immediate post-operative period, after emergency partial gastrectomy had been undertaken.

Acute ulcer. The following criteria have determined this classification in 96 patients. 1. *Gastroscopic examination.* Twenty-four patients were investigated by gastroscopy within a week of admission. Two were considered normal; the remainder showed varying degrees of mucosal abnormality. Superficial gastritis was present in 14 patients, and erosions were seen in association with gastritis in six. In 10 patients shallow subacute ulcers were identified, usually as single

lesions, or in groups of two or three showing various stages of healing. 2. *Operation and necropsy.* Acute ulceration was confirmed at operation in nine patients, and at necropsy in five. 3. *Positive radiological evidence.* The presence of an ulcer crater, without deformity of the duodenal cap, enabled a confident radiological diagnosis of acute duodenal ulcer to be made in three patients in whom subsequent X-rays showed normal appearances. 4. *Negative radiological findings.* In 77 patients the negative result of barium-meal examination, made two to three weeks after haemorrhage had ceased, allowed the presumptive diagnosis of acute peptic ulcer.

Associated diseases included chronic bronchitis (three cases), mitral stenosis (two), coronary heart disease (two), alcoholism (two), pulmonary tuberculosis (one), pneumonia (one), cirrhosis of the liver (one), diabetes mellitus (one), and psychoneurosis (one case). A history of previous aspirin medication was obtained in six patients. One patient was under treatment with phenylbutazone for rheumatoid arthritis. Five patients died: one in the fourth week after operation from pulmonary embolism; a second from carcinomatosis and chronic lung disease; cirrhosis and coronary heart disease were complicating factors in a third; diabetes and congestive heart failure in a fourth; while the fifth death was directly attributed to the effects of haemorrhage.

Post-operative bleeding. Of the 10 patients in this group, gastroenterostomy had been done for duodenal ulcer in seven; three patients with duodenal ulcer had undergone partial gastrectomy. Operation showed chronic duodenal ulcer as the site of bleeding in two patients, and anastomotic ulcer in two.

Other causes. Seven patients were shown by subsequent X-ray examination to have hiatus hernia and reflux oesophagitis, and haemorrhage was presumed to have originated in that site. Four patients had carcinoma of the stomach, confirmed at operation. Only one example of bleeding from oesophageal varices was encountered. Investigation indicated splenic vein thrombosis, and treatment was by splenectomy. Various rarities completed the series.

The age and sex distribution. Of the 238 patients studied, 127, or rather more than half, were over 50 years old, and 63, or rather more than a quarter, were over 60. The usual male preponderance was found in the chronic ulcer group, namely 96 men to 20 women, acute peptic ulcer being relatively more common in women (54 men and 42 women), the distribution in both groups being similar to that found by Jones (1952).

The length of history of dyspepsia preceding haemorrhage supported the eventual diagnosis. One hundred and two of 116 patients with chronic ulcer had had dyspepsia for more than one year; of the 96 patients in the acute ulcer group 53 had had symptoms for less than one month.

Procedure

The modern régime for the treatment of haematemesis was followed in every patient, with early liberal feeding (Meulengracht, 1935; Witts, 1937), adequate blood transfusion, and sedation as required. Shortly after admission a Ryle's

tube was passed through the nose and secured to the cheek; where feasible the position of the tip of the tube was assessed radiologically and adjusted to the angulus, a procedure impracticable in the acutely ill patients. Approximately 5 ml. of stomach contents were aspirated hourly and kept in stoppered bottles at room temperature. When 24 samples had been obtained determinations of pH were made on the unfiltered gastric contents with a sealed glass electrode. The tube was left *in situ* for periods ranging between 48 and 72 hours, aspirations being continued for at least 12 hours after blood-staining had ceased. The

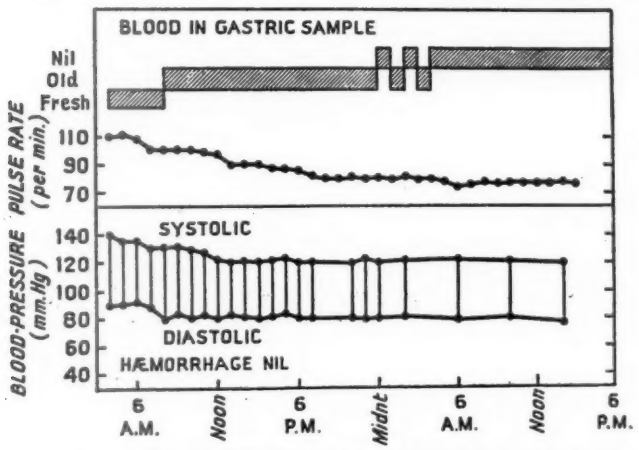

FIG. 1. Results of hourly gastric aspiration in a patient with a gastric ulcer. After initial fresh blood-staining, the samples contained old blood, and finally became clear, indicating cessation of bleeding. (Reprinted from *Lancet*, 1953, **2**, 1170, by kind permission of the Editor.)

presence of recent or old blood-staining in the aspirated specimens was recorded on a chart, on which measurements of pulse rate and blood-pressure were also plotted, together with the amounts of transfused blood and episodes of further haemorrhage. In this way a continuous record of progress was readily available at the bedside. No evidence was obtained to suggest that the presence of an indwelling tube stimulated recurrence of bleeding or favoured its continuance. The patients tolerated the procedure well, and the mortality rate was not adversely affected. Barium examination was performed after two weeks, and gastroscopy in the first week after admission was undertaken in 37 patients, without ill effect. In the remainder of the patients verification of the cause of bleeding was obtained either at operation or at necropsy.

Value of Gastric Aspiration

The finding of fresh blood in the gastric specimens aspirated at hourly intervals from admission is to be expected in the early stages after gastroduodenal haemorrhage. The usual course of events in patients whose recovery is rapid and uneventful is shown in Fig. 1. In such patients blood-staining of the gastric

samples diminishes in intensity, and appears older and darker, until the samples are finally returned clear. Blood-staining of some or all of the aspirated specimens was usual in patients with chronic gastric ulcer (28 of 40), was less frequently observed in acute ulcer (46 of 96), and was least common in chronic duodenal ulcer (34 of 76). The bedside observation of blood-staining of the aspirated gastric contents was found to be of some value in localizing the source of bleeding.

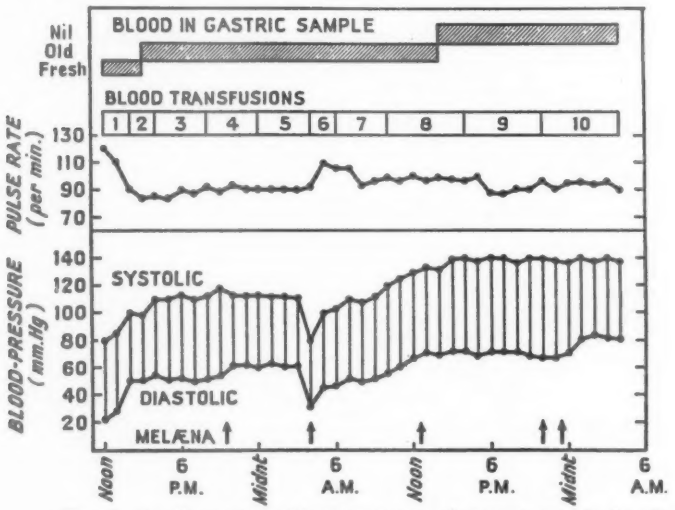

FIG. 2. A patient with a bleeding duodenal ulcer studied by hourly gastric aspiration. Although bleeding was obviously continuing (judged by pulse rate, melaena, and the necessity for continued transfusion), gastric samples rapidly became clear, indicating that the source of haemorrhage was distal to the stomach. (*Lancet*, 1953, 2, 1170.)

Evidence about the site of ulcer was obtained in 10 patients, of whom five had been admitted because of haematemesis rather than melaena. In the other five bleeding had been confined to the passage of black stools. In these 10 patients, though bleeding continued with the passage of frequent tarry motions, the gastric samples became rapidly clear of blood, indicating that the site of haemorrhage was distal to the pylorus. All these patients had duodenal lesions, and four required surgery for their eventual control. Fig. 2 illustrates the findings in a patient in whom continued melaena necessitated the transfusion of 10 pints of blood in the first two days after admission; the gastric aspirations showed only old blood by the third hour, and later cleared completely. The association of clear gastric specimens with evidence of continued loss of blood indicates that the source of bleeding lies beyond the stomach. The procedure of hourly gastric aspiration is also of value in the early detection of recurrent haemorrhage. The warning of this serious threat to life has been signalled in some patients by the reappearance of fresh blood in the aspirated specimens often many hours before other criteria (pulse-rate and blood-pressure) have indicated relapse (Table II). Haemorrhage recurred in 11 of 40 gastric ulcer patients, and was heralded by

blood-stained aspirations in 10. Blood-staining of the stomach contents provided the first evidence of recurrent haemorrhage in 10 of 12 patients in the acute ulcer group (96 patients) who bled again. Of 76 patients with chronic

TABLE II

Value of Aspiration in Anticipation of Recurrent Haemorrhage

Diagnosis	*Number with recurrent haemorrhage*	*First evidence of recurrent haemorrhage*		*No warning of recurrent haemorrhage*
		Blood-stained aspiration	*Blood-pressure or pulse-rate change*	
Chronic gastric ulcer 40	11	10	0	1
Chronic duodenal ulcer 76	14	3	2	9
Acute ulcer 96	12	10	0	2
Total 212	37	23 (62%)	2 (6%)	12 (32%)

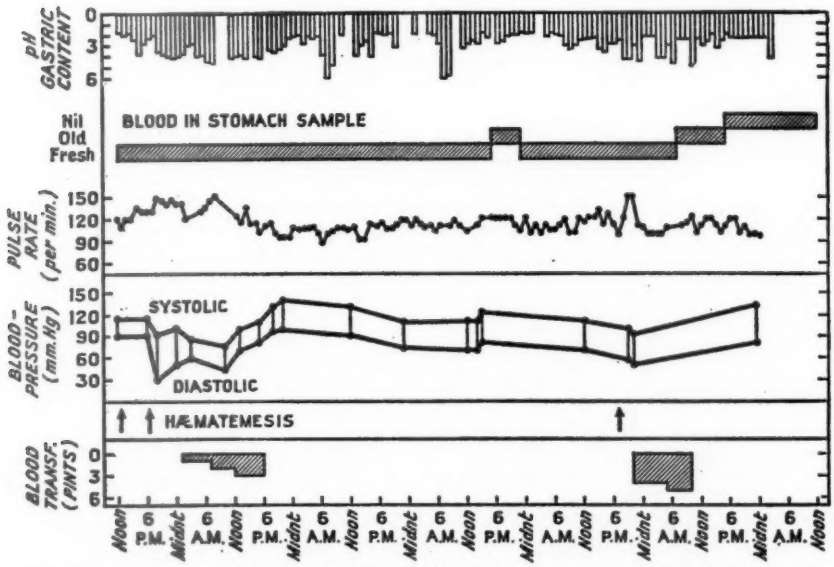

FIG. 3. Hourly gastric aspiration in a patient bleeding from a chronic gastric ulcer; after two haematemeses on the first day, clinical criteria suggested that bleeding had ceased; but copious amounts of fresh blood were aspirated in the next three days, and anticipated by many hours the third haematemesis on the fifth day. (*Lancet*, 1953, **2**, 1170.)

duodenal ulcer, recurrent haemorrhage developed in 14, but blood-staining of the gastric aspirations anticipated this complication in only three. The procedure proved most useful in patients with acute and chronic gastric ulcers, and of least value in those with duodenal lesions. In 24 patients a mild return of bleeding, as shown by aspirations, occurred in the absence of overt recurrent haemorrhage. The patient whose chart is shown in Fig. 3 was bleeding from a

chronic gastric ulcer. After twice vomiting blood on the first day, he appeared to improve with the transfusion of three pints of blood. Although there was no further evidence of massive haemorrhage during the next three days, blood was consistently present in the aspirated specimens, and preceded by many hours the haematemesis on his fifth day in hospital.

Changes in Acidity of Gastric Contents after Haematemesis

Changes in gastric acidity were estimated by 24-hour gastric analyses in the

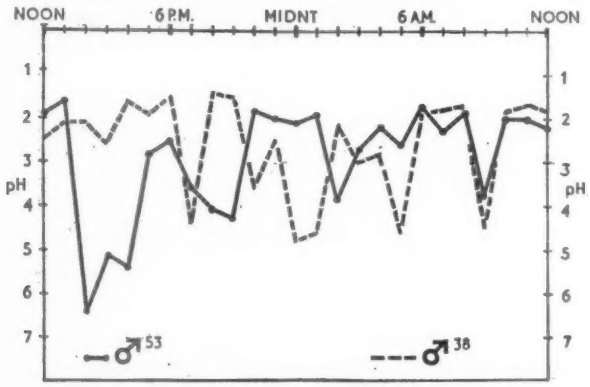

FIG. 4. Normal levels of night acidity in two patients bleeding from chronic peptic ulcer (a man aged 53 and a man aged 38 years).

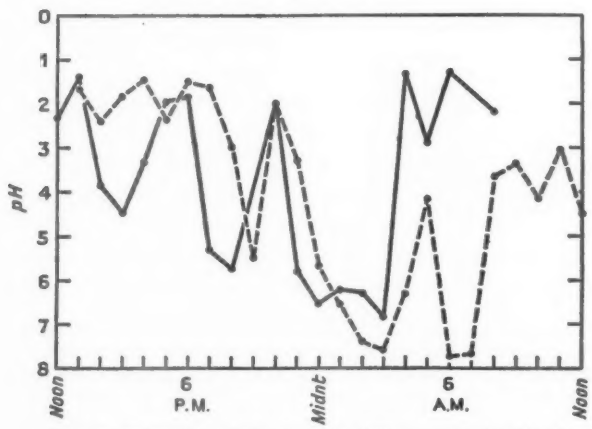

FIG. 5. Reductions in nocturnal acidity, approximating to alkaline levels, in two patients bleeding from chronic gastric ulcer. (*Lancet*, 1953, **2**, 1170.)

acute stages of gastroduodenal haemorrhage. Four types of secretion pattern were recognized: 1. *Normal night acidity*, where the recorded pH of nocturnal specimens (10 p.m. to 6 a.m.) was between 2·0 and 4·5. Fig. 4 shows this finding

in two patients. 2. *Nocturnal neutralization*, where the pH of more than two night specimens was more alkaline than 5·5. Two examples are shown in Fig. 5. 3. *High night acidity*, where pH values more acid than 2·0 were maintained in

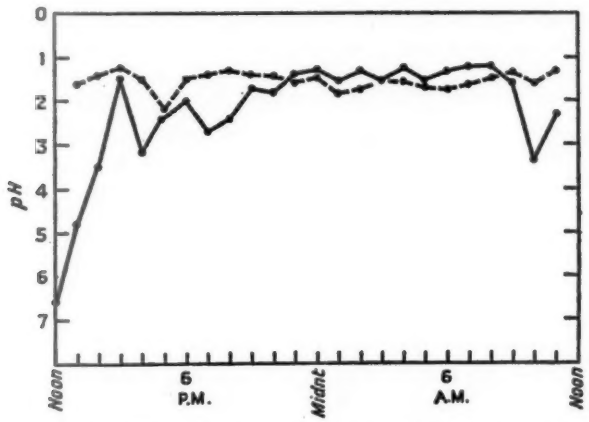

FIG. 6. High night acidity in two patients bleeding from chronic duodenal ulcer. (*Lancet*, 1953, **2**, 1170.)

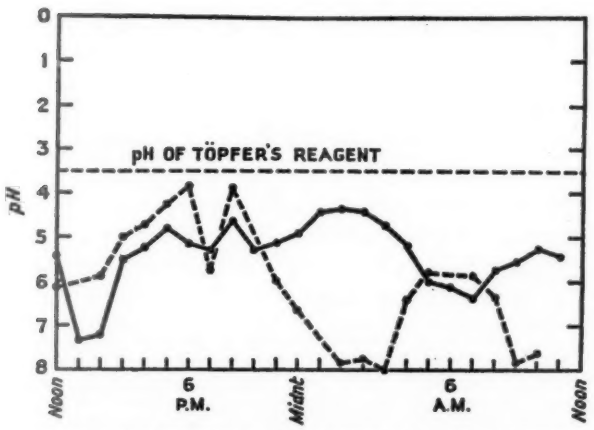

FIG. 7. Achlorhydria (pH persistently above 3·5) throughout 24 hours in two patients bleeding from acute peptic ulcer. (*Lancet*, 1953, **2**, 1170.)

more than six of the night specimens. Fig. 6 illustrates two examples of this type. 4. *Achlorhydria*, where pH values more alkaline than 3·5 were maintained through 24 hours. Two such examples are shown in Fig. 7. The finding of acid in the last few specimens of the test period is not uncommon, and succeeded initial achlorhydria in 17 patients.

Of the 238 patients studied, 212 were finally considered to have bled from

peptic ulcer, either acute or chronic. The frequency distribution of secretion patterns in these 212 patients as between gastric, duodenal, and acute ulcers is shown in Fig. 8. Of 68 patients showing high night acidity, 57 proved later to have chronic duodenal lesions; 26 of 33 patients with nocturnal neutralization had chronic gastric ulcers; and, most significant of all, the finding of achlorhydria distinguished acute ulcers, as 69 of 78 patients showing lack of acidity

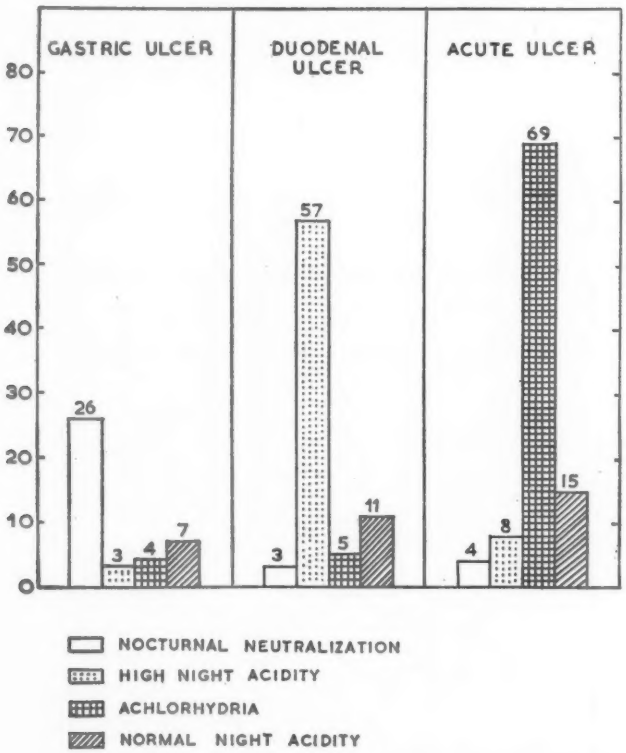

FIG. 8. Relation of secretion pattern to ultimate diagnosis. Most of the patients bleeding from chronic gastric ulcer showed nocturnal neutralization, whereas high night acidity preponderated among those with duodenal ulcer. A significant proportion of patients with bleeding acute ulcer had achlorhydria.

were found to have bled from acute lesions. Of seven patients with oesophageal hiatus hernia, two had high nocturnal acidity, four had achlorhydria, and one had normal night acidity. The achlorhydria that occurred in six of 10 patients in the post-operative group was clearly of no significance, and reflected only the disturbance in gastric function after operation. Three of four patients with gastric carcinoma showed achlorhydria, and the fourth had normal night acid values. The patient who bled from oesophageal varices showed normal night acidity. The finding of normal night acidity in 33 of the 212 patients in the ulcer

group did not prove of diagnostic importance, being evenly distributed among the various types. The reliability of the abnormal secretion patterns in the remaining 179 patients is indicated in Table III, a correct diagnosis being achieved in 152 (85 per cent.). Statistical analysis shows that the proportions in which a correct diagnosis was achieved were significantly greater than would have occurred by chance. Of the secretion patterns observed, achlorhydria proved the best basis for prediction, giving a correct diagnosis of acute ulcer in 88 per cent. of cases; high nocturnal acidity correctly indicated chronic duodenal ulcer in 84 per cent., and nocturnal neutralization indicated chronic gastric ulcer correctly in 79 per cent.

TABLE III

Accuracy of Prediction of Final Diagnosis by Initial Secretion Patterns

Secretion pattern	*Proportion with correct diagnosis*	*Percentage accuracy*
Nocturnal neutralization . .	$\frac{38}{48}$	79%*
High night acidity . . .	$\frac{57}{68}$	84%*
Achlorhydria	$\frac{57}{65}$	88%*
Total	$\frac{152}{179}$	85%*

* Results tested by standard error of difference of proportions and found to be highly significant ($P < 0{\cdot}001$).

The difference between the groups is clearly shown by calculating the mean pH values observed at each hour in the patients studied. Hunt (1952) has described averages of pH values as 'means of the negative logarithm of hydrogen ion concentration which have no physiological or clinical meaning'. Whatever may be the mathematical limitations of these values, they serve as efficient units of comparison between the groups of patients. In Fig. 9 the hourly mean pH values have been calculated, together with the standard error of the observations. The most acid values were present in patients with chronic duodenal ulcer, and ranged between pH 2·38 (standard error of mean (S.E.) $\pm 0{\cdot}13$) and pH 3·47 (S.E. $\pm 0{\cdot}19$), with high nocturnal acidity; at no time was a pH more alkaline than 3·5 observed. In the patients with chronic gastric ulcer achlorhydric values ranging between pH 3·93 (S.E. $\pm 0{\cdot}29$) and pH 4·39 (S.E. $\pm 0{\cdot}27$) were observed at night, coinciding with nocturnal neutralization in the majority. Patients with acute ulcer showed mean values significantly more alkaline than pH 3·5 at all hours, ranging between pH 4·16 (S.E. $\pm 0{\cdot}15$) and pH 5·02 (S.E. $\pm 0{\cdot}18$). Further group variations can be demonstrated by comparison of the number of hours when pH values more alkaline than pH 3·5 were recorded. Patients with chronic duodenal ulcer were achlorhydric for a mean of 7·39 hours (S.E. $\pm 0{\cdot}76$), with chronic gastric ulcer for a mean of 11·27 hours (S.E. $\pm 1{\cdot}10$), and with acute ulcer for a mean of 17·71 hours (S.E. $\pm 0{\cdot}73$). The application of Student's t test to these data shows highly significant differences between the patients with acute lesions and those with chronic duodenal ulcer ($t = 9{\cdot}79$, $n = 170$, $P < 0{\cdot}001$), and between those with acute and those with chronic

gastric ulcer ($t = 4{\cdot}83$, $n = 134$, $P < 0{\cdot}001$), and significant differences between the two groups of chronic ulcer patients ($t = 2{\cdot}94$, $n = 114$, $P < 0{\cdot}01$). Of 24 patients initially achlorhydric at the time of haemorrhage, 20 showed a return of acid secretion. Fig. 10 demonstrates this change in two patients.

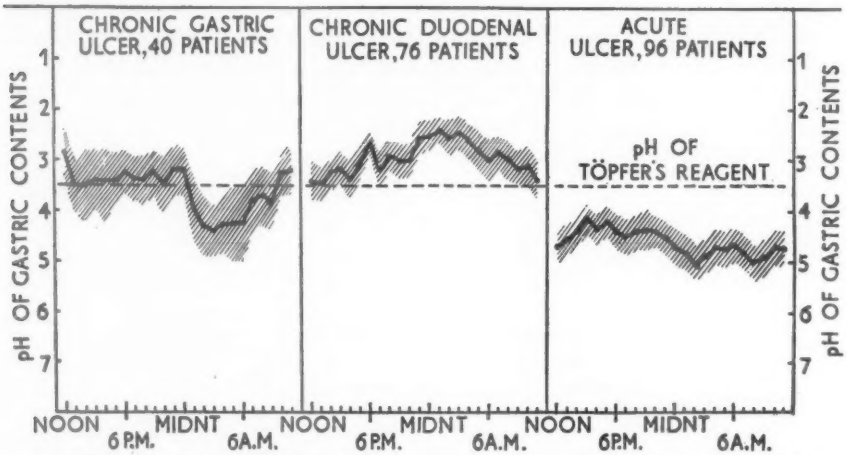

FIG. 9. Mean hourly changes of acidity, with standard error, in 212 patients bleeding from acute or chronic peptic ulcer. The shaded area indicates variation attributable to chance (twice the standard error of the mean).

Note the highest nocturnal acidity in patients with chronic duodenal ulcer, in contrast with low nocturnal acidity in those with chronic gastric ulcer. In patients with acute ulcer the mean pH values are significantly more alkaline than 3·5 at all hours.

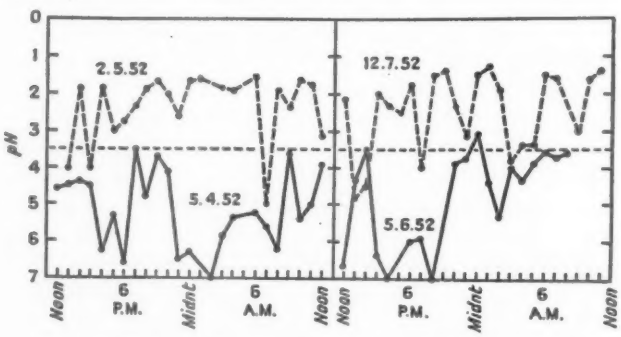

FIG. 10. Return of acid secretion in two patients with acute ulcers who were initially achlorhydric at the time of haemorrhage. (*Lancet*, 1953, **2**, 1170.)

Possible Causes of Achlorhydria during Bleeding from Acute Peptic Ulcer

Buffering action of blood. The finding of achlorhydria in bleeding peptic ulcer has not previously been described; neutralization of the stomach contents with blood appeared to be of importance, and was first investigated. Fresh heparinized self-donated blood was introduced in measured quantities through an

indwelling Ryle's tube into the stomach of a healthy male subject. Samples of gastric contents were withdrawn at intervals of five minutes, and the pH of these unfiltered specimens estimated with a glass electrode. The isolated introduction of a large quantity of blood produced only a short-lived achlorhydria, but the repeated instillation of moderate amounts caused a more uniform depression of gastric acidity, approximating to achlorhydria (Fig. 11). It is possible that

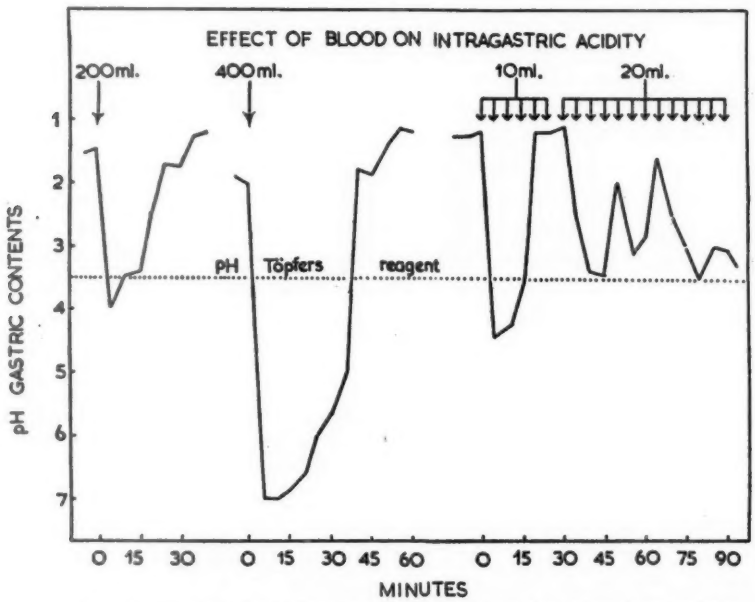

FIG. 11. The effect of introduction of blood into the stomach on gastric acidity: large quantities produce only temporary achlorhydria, whereas repeated introduction of smaller amounts causes a more uniform depression of gastric acidity.

slow oozing of blood from submucosal vessels, which may occur in acute ulcer, is a more effective neutralizing force than the intermittent arterial bleeding more likely to complicate chronic ulcer. Achlorhydria was observed as frequently in 104 patients from whom gastric aspirations remained clear throughout the initial 24 hours as in 108 patients in whom blood-staining of some specimens was observed, namely in 34 per cent. and 39 per cent. respectively, proportions which do not differ statistically (Fig. 12). In the chronic ulcer group similar proportions of patients, with and without blood-staining of the gastric contents, were achlorhydric (6 per cent. and 9 per cent. respectively); in the acute ulcer group the proportions differed by a barely significant degree (83 per cent. and 62 per cent.). The neutralizing effect of blood cannot, therefore, wholly account for the production of achlorhydria; it is possibly effective only when secretion is reduced or suppressed, as in bleeding acute ulcer, and exerts little action in haematemesis from chronic ulcer, where acid secretion is maintained.

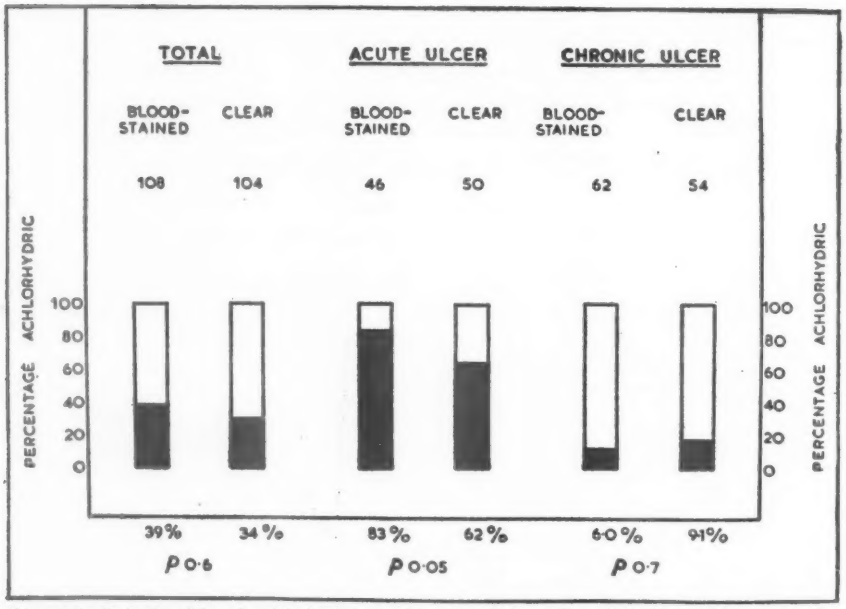

FIG. 12. Relationship of achlorhydria to blood-staining of aspirated gastric samples in the total ulcer group and in the acute and chronic ulcer groups. The proportions of achlorhydric patients with and without blood-staining of the gastric contents were similar in each case.

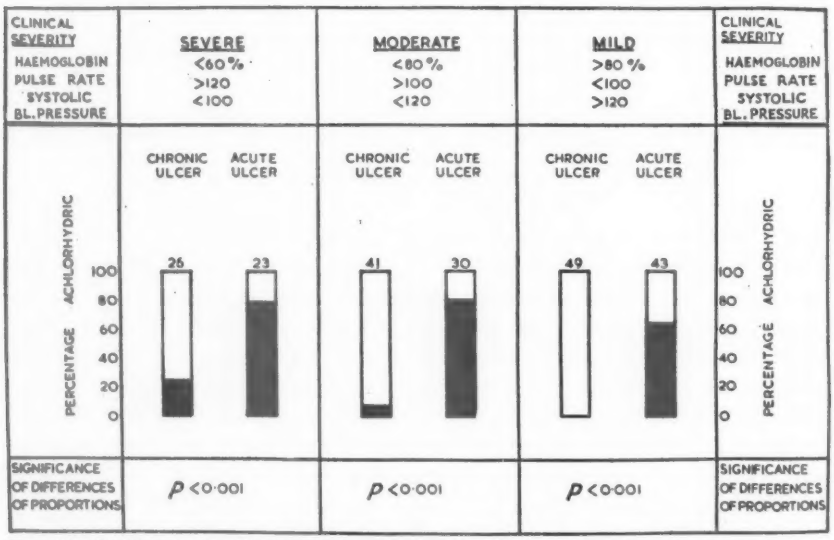

FIG. 13. Incidence of achlorhydria in patients severely, moderately, and mildly shocked on admission, compared in patients bleeding from acute and those bleeding from chronic ulcer. At all degrees of severity achlorhydria is significantly more common in the acute ulcer group.

Effect of shock, anaemia, and biochemical changes consequent upon the haemorrhage. It seemed possible that parietal-cell function might be adversely affected in peripheral circulatory failure. Barclay and Bentley (1949) demonstrated a layer of vessels in the submucosa of the stomach through which blood can be shunted so as to leave the mucous membrane anaemic, especially under conditions of nervous stress. Alvarez (1949) considered that the sudden formation of peptic ulcers, especially of the acute penetrating or perforating type, could be attributed to this cause. The effect of shock on the genesis of achlorhydria was therefore investigated. In Fig. 13 the incidence of achlorhydria has been compared in patients bleeding from acute and chronic peptic ulcer who were severely, moderately, and mildly shocked on admission. Clinical assessment of severity on admission proved more satisfactory than comparison of the amounts of blood transfused, which, besides indicating the requirements of resuscitation on admission, reflected also the number and severity of recurrent haemorrhages. Blood-pressure, pulse-rate, and haemoglobin levels formed the basis for the assessment of the degree of shock on admission. It is obvious that the degree of shock cannot explain highly significant differences in the incidence of achlorhydria between the acute and chronic ulcer groups, namely 78 per cent. and 23 per cent. in patients severely shocked, 80 per cent. and 7 per cent. in those moderately shocked, and 63 per cent. and nil in those mildly shocked. In both groups achlorhydria became more common with increasing severity of shock, its frequency changing in the chronic ulcer group from nil to 7 per cent. to 23 per cent., and in the acute ulcer group from 63 per cent. to 80 per cent. to 78 per cent. Tests for linear trends show very significant increases in the incidence of achlorhydria in the chronic ulcer group with greater degrees of shock ($P < 0{\cdot}001$), and suggest that even in this group achlorhydria can be induced if circulatory changes in the mucosa are sufficiently great. In the acute ulcer group some factor additional to shock must be implicated to explain the high frequency of achlorhydria when shock is minimal.

Anaemia and biochemical changes. The effect of anaemia on gastric acid secretion has been the subject of a number of clinical and experimental studies (Ogilvie, 1935; Alvarez and Vanzant, 1936; Apperly, 1936; Monaghan, Bockus, Kornblum, and Moffitt, 1936; Hallen, 1938) which concluded that there was a close association between defective secretion of hydrochloric acid and the various types of anaemia. The influence of plasma-bicarbonate and blood-urea levels on gastric acid secretion has been investigated with conflicting results (Browne and Vineberg, 1932; Apperly, 1936; Kurtz and Clark, 1947). In the present investigation of gastric acid secretion after haematemesis the levels of haemoglobin, plasma bicarbonate, and the blood urea nitrogen were estimated as a routine on admission of the patients, but appeared in no way to be related to the abnormal secretion patterns obtained.

Age and sex differences. The difference in age and sex incidence between patients with acute peptic ulcers and those with chronic lesions is well known; the age and sex distribution of patients studied in the present investigation resemble those of larger reported series. Davies and James (1930), using

fractional test meal analysis, failed to find free acid in 32 out of 100 normal persons aged over 60. Vanzant, Alvarez, Eusterman, Dunn, and Berkson (1932) investigated the secretory capacity of 3,746 patients without evidence of disease in the digestive tract, and showed that from youth to the age of 65, in both sexes, there was a straight-line correlation between the incidence of achlorhydria and the age of the subject. At all ages women showed a greater tendency to achlorhydria than men, a difference of about 3 per cent. on the scale used. In women the incidence of true achlorhydria varied from 3 per cent. at 20 years to 28 per cent. at 60 years. In men the corresponding values were 0 at 20 years and 23 per cent. at 60 years. The increasing incidence of achlorhydria with advancing age might suggest that age and sex are factors which must be taken into account when considering the significance of abnormal secretion patterns. In the present series, of 54 men with acute ulcer and achlorhydria, 43 were aged less than 60, and 20 less than 40 years. Of the 42 women with acute ulcer and achlorhydria, 30 were aged less than 60, and 11 less than 40 years. These figures afford strong evidence that in the patients described in this investigation the finding of achlorhydria was not related to age.

Acute Gastritis

There remains the hypothesis that a basic difference in gastric secretory capacity exists between patients with acute and those with chronic lesions, a difference which is ultimately responsible for the types of secretion pattern observed in bleeding peptic ulcer. Though absolute proof is lacking, several considerations lend strong support to the view that acute ulcer, chronic gastric ulcer, and chronic duodenal ulcer are separate diseases of different pathogenesis. James and Pickering (1949) using 24-hour gastric analyses, presented their conclusions with regard to chronic gastric and duodenal ulcers. Their findings were consistent with the hypothesis that chronic duodenal ulcer is related to an abnormally high intragastric acidity, but they were unable to show that a similar explanation held good for gastric ulcer. Card and Marks (1958) showed that it was possible to establish a strong correlation between parietal-cell mass and acid output; similar conclusions were reached by Hunt and Kay (1954) after studying the secretory response to maximal histamine stimulation in normal subjects and patients with duodenal ulcer. The observations described here provide further strong support for their views, and indicate that recent or continuing bleeding from chronic gastric and duodenal ulcers does not significantly distort the typical pattern of acid secretion seen in the uncomplicated disease.

Relation of achlorhydria to gastritis. Causes of achlorhydria in various forms of gastric disease have constituted the basis of numerous studies. Ewald (1886) noted complete absence of free acid in the presence of total atrophy of the gastric mucosa, and Einhorn (1892) observed 'achylia gastrica' as the main symptom 'of the affection heretofore described under the heading of "atrophy of the stomach"'. Martius (1897) held that lack of acidity was a constitutional abnormality, a belief modified by Hurst (1934), who thought that it was the

conjunction of gastritis with the hyposthenic gastric constitution that led to achlorhydria. Faber (1935) considered that diminished secretion of acid was the classical sign of chronic gastritis. Guiss and Stewart (1948) showed that the production of hydrochloric acid was directly proportional to the number of normal-appearing parietal cells present, and concluded that the degenerative changes of chronic atrophic gastritis were the basic cause of hypochlorhydria and achlorhydria in gastric disease. Swalm, Jackson, and Morrison (1936), Bank and Renshaw (1939), Schindler and Murphy (1940), and Findley, Kirsner, Palmer,

TABLE IV

Correlation of Gastroscopic Appearances and Gastric Secretion Findings in 24 Patients with Acute Ulcer

Mucosal changes	*Number of cases*	*Initial gastric analysis*		*Later analysis*		
		Achlorhydric	*Not achlorhydric*	*Achlorhydria persisting*	*Acid secretion returning*	*Not done*
Atrophic	9	9	..	4	2	3
Not atrophic	15	8	7	..	8	..
Acute ulcers:						
Present	14	9	5	1*	7	1
Absent	10	8	2	3*	3	2
Superficial gastritis:						
Present	14	11	3	1*	7	3
Absent	10	6	4	3*	3	..

* Atrophy present in addition.

and Pullman (1949) showed a close association between atrophic gastritis and the incidence of achlorhydria. More recently, Doig and Wood and their colleagues (Wood, Doig, Motteram, Weiden, and Moore, 1949; Doig and Wood, 1952 *a*, *b*, 1958; Motteram, 1951; Funder and Weiden, 1952; Joske, Finckh, and Wood, 1955) have studied the relationship between the secretions of the gastric mucosa and its morphology, biopsy specimens being obtained by means of a flexible vacuum-tube instrument. They found a direct correlation between the extent of atrophy and the volume, concentration of free acid, and pepsin content of gastric secretion after histamine stimulation. In superficial gastritis histamine test meals showed diminished or absent acid, and a reduction in pepsin values. When gastritis was associated with moderate to severe atrophy there was always a histamine-fast achlorhydria, with diminished pepsin secretion.

In the present investigation 24 patients, finally diagnosed as having bled from acute ulcers, were examined by gastroscopy within a few days of their admission to hospital. All but two showed signs of mucosal abnormality. In 14 patients the characteristic appearances of superficial gastritis were found, with irregular patchy hyperaemia and flecks of adherent white mucus, and in five of these patients areas of chronic atrophic gastritis were scattered through the superficial inflammatory lesion. Diffuse atrophy was present in a further four patients, without evidence of superficial gastritis. Mucosal erosions, usually numerous and occasionally scattered over the entire stomach, were observed in

association with gastritis in six patients, and small shallow subacute ulcers, in various stages of healing, were identified in 10. Of 22 patients in whom gastroscopy revealed unmistakable mucosal disease, 17 had achlorhydria judged by the 24-hour gastric analyses done in the acute stage of the illness. The two patients in whom no mucosal abnormality was seen at gastroscopy showed normal levels of acid secretion. The detailed findings are shown in Table IV, which correlates gastroscopic appearances with the frequency of achlorhydria. Of the three facets in the gastritic process, namely atrophy, acute ulceration, and superficial gastritis, atrophic change seemed the most important factor in determining achlorhydria and favouring its persistence. In four patients with persistent achlorhydria atrophic change was the major abnormality. Superficial gastritis frequently determined acute achlorhydria; 11 of 14 patients initially showed this change, but achlorhydria persisted in only one of eight patients in whom tests were repeated; this subject showed well-marked atrophic change in addition to gastritis. Similarly, acute ulceration induced short-lived achlorhydria in nine of 14 patients, but acid secretion returned in all but one subject, who also showed evidence of gastric atrophy.

It therefore appears that both acute and chronic gastritis may manifest themselves by upper gastrointestinal bleeding, and that achlorhydria is to be expected at the time of haemorrhage. When acute gastritis exists independently of chronic mucosal disease, recovery of normal function is the rule. Chronic gastritis, on the other hand, may at any time explode into an acute haemorrhagic exacerbation, but recovery of functional and morphological normality is rarely possible, achlorhydria persists, and the chronic inflammatory and atrophic changes advance.

Gastritis as a cause of haemorrhage. In Palmer's (1954) study of gastritis one of the more important clinical manifestations encountered was haematemesis. Of 70 patients with a gastroscopic diagnosis of chronic atrophic gastritis, none had ever vomited blood, although some had had melaena. Sixteen of 83 patients diagnosed as having superficial gastritis, and 63 of 190 patients with hypertrophic gastritis, gave histories of haematemesis. Findley, Kirsner, Palmer, and Pullman (1949) obtained a history of upper gastrointestinal bleeding in 4 per cent. of patients with gastric atrophy, in 8 per cent. with superficial gastritis, and in 12 per cent. of patients judged to have hypertrophic gastritis. Rodgers and Jones (1938), in 600 gastroscopic examinations for unexplained dyspepsia or recent haemorrhage, observed that small, shallow, subacute ulcers were often found in association with a thin atrophic gastric mucosa. In these patients the fractional test meal showed either absent or diminished acid secretion. The clinical importance of acute gastric ulcer and erosive gastritis as a cause of haematemesis has been emphasized by Jones (1956). Five hundred and fifty-nine of 1,910 patients admitted with upper gastrointestinal bleeding were assigned to this 'acute lesion' group; three hundred and three were examined by gastroscopy, and 111 acute gastric ulcers demonstrated. A diagnosis of acute gastritis was made in only seven patients, but Jones commented that more examples of acute gastritis would be recognized if gastroscopy were done within

one or two days of admission. In Fraenkel and Truelove's (1956) series of 540 admissions for haematemesis, 15·6 per cent. of cases were accounted for by acute peptic ulcer. Tanner (1954) considered gastritis to be the cause of bleeding in 97 of 1,490 patients admitted for massive haematemesis and melaena between 1941 and 1953.

Mucosal injury from drugs is a possible cause of gastric erosion and bleeding. The harmful effect of aspirin on the gastric mucosa was studied by Douthwaite and Lintott (1938), and more recently by Muir and Cossar (1955). Hurst (1943) believed that aspirin was the major cause of bleeding in at least one-half of patients suffering from upper gastrointestinal haemorrhage in whom other obvious causes had been eliminated. In the present investigation aspirin was thought to be an important factor precipitating bleeding in four patients out of 24 who were investigated by gastroscopy. In one patient phenylbutazone was responsible for an acute erosive gastritis with haematemesis, and an alcoholic excess was incriminated in another. It is clear that acute ulceration or erosion of the stomach is a common lesion, accounting for about one-quarter of admissions for haematemesis.

Practical Application of the Findings

There were 11 deaths among the 238 patients admitted urgently with haematemesis and melaena and studied by immediate hourly gastric aspiration, a mortality rate of 4·7 per cent., which compares favourably with larger series (Jones, 1952; Tanner, 1954). Serious associated complications were present in the majority of the fatal cases. Of the 28 patients submitted to emergency gastrectomy for uncontrolled bleeding, four died. Severe recurrent haemorrhage may demand operation even though a pre-operative diagnosis of acute peptic ulceration has been made, based on the finding of achlorhydria. Nine patients bleeding from acute ulcers required surgery, with one death, which occurred in the fourth week after operation from pulmonary embolism. Ten patients bleeding from chronic duodenal ulcer underwent emergency gastrectomy, with three deaths. There were no post-operative fatalities in the seven patients with chronic gastric ulcers submitted to emergency surgery.

The results obtained by early aspiration after haematemesis have provided clear evidence of its value, notably in the management of patients who bleed again after admission to hospital, and also in the facilitation of earlier diagnosis of the cause of bleeding. The procedure allows prompt recognition of recurrence or continuance of bleeding. In some patients the site of the haemorrhage can be inferred from the association of continuing melaena with clear aspirated specimens. This association was seen in 10 patients in the present series, all of whom were ultimately found to have bled from duodenal lesions. The simple bedside observation of blood-staining can provide reliable information both about recurrent bleeding and about the ulcer site, and justifies Kinsella's (1950) advocacy of its wider application in clinical practice. The changes observed in intragastric pH immediately after haemorrhage have been of diagnostic value

in 152 of the 179 patients (84·9 per cent.) in whom the secretion patterns were abnormal. From knowledge of the secretion patterns obtained in individual patients bleeding from an unknown lesion in the upper gastrointestinal tract a more confident assumption could be made as to the pathological basis of the illness than would otherwise have been possible. In the case of haemorrhage from acute peptic ulcer the recognition of achlorhydria provided an indication for continued medical treatment.

In the light of the experience gained from this investigation the practical applications of the findings have been embodied in the following scheme for the management of haematemesis. On the patient's admission blood is withdrawn for grouping and haemoglobin estimation. Early liberal feeding and adequate blood transfusion are given, but morphine is withheld unless specially indicated. A gastric tube is passed through the nose as soon as the patient has been made comfortable; 5 ml. of stomach contents are aspirated at hourly intervals by syringe suction, and the samples kept in numbered and stoppered bottles at room temperature. The presence or absence of fresh or old blood in the aspirated specimens is recorded on a chart, together with measurements of pulse rate and blood-pressure, episodes of further bleeding, and the times and amounts of blood transfusions. House officers are informed immediately if the hourly aspirations indicate recurrence of bleeding, so that, when necessary, preparations for blood transfusion can be made and surgical consultation obtained. Aspiration of the stomach is continued for at least 24 hours, and if possible for 12 hours after bleeding has ceased. The pH of these samples is estimated with a glass electrode, and a graph of intragastric acidity constructed, showing changes of pH throughout the 24 hours of the test period. At this stage, on the patient's second day in hospital, the case is reviewed, with particular regard to the information obtained by aspiration. The finding of high night acidity or nocturnal neutralization indicates the likely presence of chronic duodenal ulcer or chronic gastric ulcer respectively, and, if evidence of recurrent or continued bleeding is provided by the appearance of the aspirated samples or by other clinical signs of haemorrhage, the surgeon on duty is asked to see the patient, especially if over 45 years of age, with a view to immediate operation. If bleeding has stopped, surgery is delayed pending further evidence of recurrence. The finding of achlorhydria is an indication for continued medical treatment, for such a pattern of gastric secretion in the early stages of haematemesis is presumptive evidence of acute peptic ulcer. Nevertheless, surgery may still be required to control bleeding in such patients; continued massive haemorrhage is an indication for surgical intervention, though this need is rarely so urgent as in bleeding chronic ulcer. In every patient all evidence of chronic peptic ulcer from previous investigation must be given due regard, in conjunction with the history before admission, in order to assist the final decision between operative and conservative treatment. Early gastroscopic investigation is an invaluable aid in confirming the findings from aspiration and 24-hour gastric analysis, and should be undertaken in any patient in whom decisive action in treatment is delayed because of doubt as to the cause of bleeding.

The importance of reaching an early decision as to the surgical treatment of haematemesis cannot be overemphasized. Rapid deterioration, in circumstances of recurrent bleeding despite apparently adequate replacement of blood by transfusion, is common, and delay in seeking surgical aid often fatal. Every patient with haematemesis presents a new challenge to diagnosis and proper management. When the physician is guided by all the facts available from the history and examination, and by the evidence obtained by immediate gastric aspiration and early gastroscopic investigation, correct appraisal is greatly facilitated. Confidence in the recovery of such patients, under either medical or surgical treatment, is usually justified by the event.

Our thanks are due to the medical and surgical staff of the United Leeds Hospitals and St. James's Hospital, Leeds, for allowing us to study patients under their care. We are indebted to Mr. G. D. Coulson and Mr. H. Revell for technical help, and to the nursing staff of both hospitals, without whose assistance the investigation would not have been possible. Professor Hartfall, Professor Tunbridge, and Dr. Maxwell Telling critically appraised the text of this paper, which was abridged from a thesis submitted by one of us (G. N. C.) for the degree of Doctor of Medicine.

Summary

1. Immediate intubation, with hourly aspiration of gastric contents, was undertaken in 238 patients admitted because of haematemesis or melaena. Aspiration proved of value in the recognition of continued or recurrent haemorrhage, and study of the acidity pattern in the acute stages of gastrointestinal bleeding led to early aetiological diagnosis in the majority of patients studied. A low overall mortality of 4·7 per cent. was achieved.

2. The bedside observation of blood-staining in gastric contents aspirated at hourly intervals proved of value in confirming the belief that bleeding had ceased, in anticipating recurrent haemorrhage, and in indicating the duodenal origin of gastrointestinal haemorrhage. Recurrent haemorrhage was most frequently anticipated by aspiration in patients with acute and chronic gastric ulcer, and the method was of least value in chronic duodenal lesions.

3. Study of secretion patterns in the initial 24-hour period of gastrointestinal bleeding showed that acid secretion of a diagnostic type was maintained in patients bleeding from chronic duodenal and gastric ulcer, but that achlorhydria was more often associated with bleeding acute ulcer. On this basis the site and type of ulcer responsible for gastrointestinal bleeding was accurately predicted in a significant proportion of the patients investigated. Of the secretion patterns observed, achlorhydria proved the best basis for prediction, giving a correct diagnosis of acute ulcer in 88 per cent. of cases; high nocturnal acidity correctly indicated duodenal ulcer in 84 per cent., and nocturnal neutralization indicated chronic gastric ulcer in 79 per cent. Differences between acute and

chronic ulcer could also be demonstrated in that the patients with acute ulcer remained achlorhydric for a significantly longer period of the initial 24 hours. When gastric analysis was repeated after haemorrhage had ceased, acid secretion returned in the great majority of patients who had bled from acute ulcer.

4. Investigations of the mechanism of achlorhydria observed in acute bleeding peptic ulcer suggest that it cannot be attributed to the neutralizing effects of blood in the gastric contents, but that it results from a temporary depression of the function of the parietal cells, induced by circulatory changes in a gastric mucosa either defective in parietal cells or acutely damaged by gastritis.

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POLYCYTHAEMIA VERA AND ITS TREATMENT WITH RADIOACTIVE PHOSPHORUS[1]

A Review of 90 Cases

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With Plates 27 and 28

Polycythaemia vera is a disease characterized by an absolute increase in the circulating red-cell mass. It is usually associated with an increase in total blood volume, and with leucocytosis, neutrophilia, and thrombocytosis. It was first described by Vaquez in 1892, and subsequently in greater detail by Osler in 1903. Türk (1904) was the first to realize the significance of the association of increased numbers of erythrocytes with the concomitant changes of the leucocytes and platelets. The primary disorder appears to be bone-marrow proliferation, and the disease has been considered to belong to the group which includes chronic myeloid leukaemia, idiopathic (agnogenic) myeloid metaplasia of the spleen and liver, myelofibrosis, megakaryocytic leukaemia, and erythroleukaemia (di Guglielmo's disease). They all appear to be a product of increased proliferation of bone-marrow cells. There is no clear-cut division among the syndromes of the group, which may coexist or merge indistinguishably into one another (Merskey, 1949; Dameshek, 1951; Wasserman, 1954). Although polycythaemia vera is relatively uncommon, it has aroused much interest, partly because of its apparent relationship with the more malignant varieties of the myeloproliferative disorders, and partly because the introduction of radioactive phosphorus (^{32}P) as a method of treatment has made the early recognition of the disease of clinical importance.

The treatment of polycythaemia vera with radioactive phosphorus at Hammersmith Hospital was started towards the end of 1949. The patients come from a very wide area, including a few from overseas. It is therefore impossible to make any estimate of the incidence of polycythaemia in the population for which this hospital provides a routine radiotherapy service. Moreover, it is impossible to assess to what extent selection has played a part in the composition of the present series. The criteria for selection have almost certainly been different at the various hospitals which referred the patients, and have altered during the

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last decade, but it is our impression that only patients with a more florid type of disease have been referred. The clinical and haematological findings in 90 patients are reviewed below, and the response to treatment in 78 patients analysed.

Clinical Findings

Age. Fig. 1 shows the age distribution in the series. The majority of cases occurred between the ages of 50 and 70 years; only six patients (6·7 per cent.) were under the age of 40. The youngest patient was 20 years old, and the oldest 86. This is in conformity with the usual finding that polycythaemia vera is a disease of the older age groups.

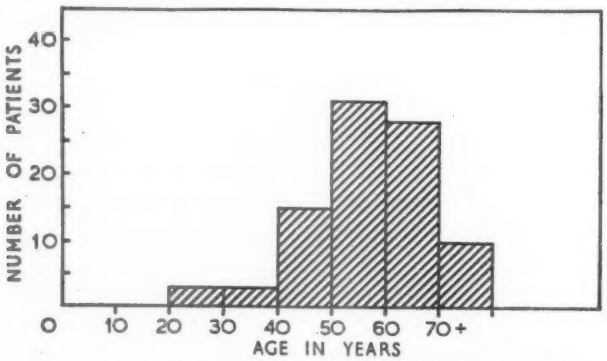

FIG. 1. Age distribution at time of first treatment.

Sex. There have been virtually equal numbers of each sex (44 men and 46 women). Most reported series show a slight male preponderance. Videbaek (1950) gave a sex ratio of 1·45:1, and Lawrence (1955) 1·3:1.

Family history. Three patients gave a history of polycythaemia or leukaemia in other members of their families, but there was no opportunity to confirm this. A family history is uncommon in polycythaemia vera, and a well-authenticated one very rare. Engelking (1920) found a family in which 11 members showed features of polycythaemia.

Onset and duration. Polycythaemia vera is an insidious disease, and it has been almost impossible to establish a definite time of onset, especially if plethora is taken as a characteristic sign of the disease. One of our patients, first seen at this hospital in 1955, said that he had been noted to have a high colour when he was a soldier in the British Army during the Boer War, 55 years before. In assessing the duration we have considered only the onset of symptoms which appear to be related to the disease. By this criterion the period between the onset of symptoms and the establishment of the diagnosis is remarkably variable—between one month and 20 years. The history most commonly extends over a period of two to five years.

Previous treatment. Thirty-five patients were treated by other methods before

being referred to this hospital for ^{32}P therapy. Twenty of them were treated for varying periods by repeated venesections, and a further five had venesections in combination with irradiation or phenylhydrazine. Eleven patients were treated by one or another of the external radiation techniques, and four had one or more courses of phenylhydrazine.

TABLE I

Incidence of Symptoms

Symptoms	*Number of patients*
Cerebral	50
Abdominal	31
Cutaneous	25
Circulatory	21
Pulmonary	20
Angina and palpitations	15
Visual	13
General	11

Symptoms

The symptoms vary greatly, but can be related, generally, to the increased blood volume, with engorgement of capillaries and increased blood viscosity, and perhaps to increased extracellular fluid. In addition, the presenting symptom may be due to a complication of the disease, such as haemorrhage or thrombosis. Table I shows the frequency of occurrence of the various symptoms. Cerebral symptoms are the most common, and include headaches, migraine, a feeling of fullness in the head, dizziness, vertigo, tinnitus, lack of concentration, and symptoms due to cerebrovascular accidents. Cutaneous lesions are also common, and include non-specific dermatitis, urticaria, acne rosacea, and recurrent leg ulcers. The pruritus associated with the disease affects the whole body, and can at times be very severe. It is usually accentuated by hot baths, and when present this is a characteristic diagnostic feature of the disease. Abdominal symptoms include anorexia, epigastric discomfort and pain, flatulence, nausea, and vomiting. The patient may be aware of an abdominal mass, and pain over the spleen due to infarction or perisplenitis is not uncommon. Visual disturbances are also frequent: they may be minor, such as spots and flashes in front of the eyes, or 'eyestrain'; but diplopia and partial or complete blindness may also occur. Under general symptoms are included a general feeling of ill health, lassitude, and malaise.

Physical signs

Facies. The great majority of patients have a characteristically red congestion of the face, and often of the fingers and toes. The degree of plethora, however, does not bear any direct relationship to the severity of the erythrocytosis, and it frequently persists after the blood count has returned to normal. Cyanosis of the extremities, and of the tips of the nose and ears, is very common, especially

in winter. Suffusion of the conjunctivae, occasionally with conjunctival haemorrhage, completes the characteristic facial appearance.

The blood-pressure was found to be raised (diastolic pressure 100 or over) in 31 patients. In the early stages of the disease this hypertension appears to be reversible. An analysis of our patients does not provide any support for the separation of a group of patients with hypertension, but without splenomegaly, known as 'polycythaemia hypertonica', or Gaisbock's disease.

Spleen and liver. Enlargement of the spleen is commonly found on palpation, but its absence does not exclude the diagnosis. At the time of their first treatment 69 patients (77 per cent.) had enlarged spleens, which in the uncomplicated cases extended from 1 cm. to 15 cm. below the costal margin. Harman, Hart, and Ledlie (1955) found splenomegaly in 56 per cent. of their cases, and Lawrence (1949) in 65 per cent., whereas Wintrobe (1956) reported this finding in 90 per cent. of his patients. Hepatomegaly is less common, and was present in 47 cases (52 per cent.). In most of these cases there was concomitant splenomegaly, and hepatomegaly alone was present in only nine patients. Lawrence (1955) found enlargement of the liver in 33 per cent. of his patients, and Wintrobe (1956) in 50 per cent.

Gastrointestinal. Glossitis, with painful ulceration of the tongue and mouth, may be found. The glossitis may be atrophic or hypertrophic, and may show fissuring of the tongue. It was found in six patients. Symptoms of 'indigestion' are common, but only in eight of our patients was the diagnosis of peptic ulcer confirmed either radiologically or at operation. The association has been known for many years, and has been commented on by various workers (Wilbur and Ochsner, 1935; Lawrence, 1955).

Gout. In the majority of cases of polycythaemia vera the level of uric acid in the blood has been reported to be normal. The association of gout with polycythaemia is, however, well recognized. It was found in five of our patients (5·6 per cent.); in all these cases the blood uric acid level was raised. These patients were treated with colchicine or probenecid, as well as with radioactive phosphorus for the polycythaemia. ^{32}P did not appear to aggravate the gout in any of the patients, but it is difficult to determine whether their favourable responses were due to specific treatment for gout or to the control of polycythaemia.

Vascular. The clinical picture may be dominated by the sequelae of haemorrhage or thrombosis. These can occur at numerous sites and give rise to a variety of physical signs. They are discussed later.

Haematological Features

Methods

Blood-volume estimations. Since 1954, blood-volume measurements have been performed with ^{51}Cr-labelled red cells, the technique being similar to that described by Mollison and Veall (1955). The red-cell mass has been obtained from the total blood-volume figure by calculation; a correction factor was applied to convert venous to whole body haematocrit values (Chaplin,

Mollison, and Vetter, 1953). In order to obtain the absolute packed-cell volume for measurement of red-cell mass, when the packed-cell volume was determined in a standard M.S.E. centrifuge, a correction was made for trapped plasma by the formula of Chaplin and Mollison (1952). In more recent determinations a microhaematocrit method was employed, and correction was unnecessary. *Peripheral blood counts.* The routine haematological investigations were carried out by standard methods as described by Dacie (1956). *Bone-marrow* smears were prepared from marrow obtained by needle biopsy of the sternum. Bone biopsies have been carried out in a number of patients by means of the Sacker–Nordin trephine, the size of which is intermediate between the Turkel trephine and standard bone trephines (Sacker and Nordin, 1954). By this means a sample is obtained of adequate size for histological section. The procedure can be carried out under local anaesthesia.

Findings

The results discussed below were obtained immediately before treatment with ^{32}P was given. As mentioned above, 11 patients had in the past received radiation therapy, and four had been treated with phenylhydrazine; all patients were in relapse when these investigations were made.

Red-cell mass and blood volume. The essential criterion for the diagnosis of polycythaemia vera is the presence of increased red-cell mass. The normal red-cell mass has been found to be approximately 30 ml. per kg. body-weight (Gray and Sterling, 1950; Brady, Cooper, Colodzin, McClenathan, King, and Williams, 1953; Berlin, Hyde, Parsons, and Lawrence, 1952). Wintrobe (1956) quoted the results obtained by several investigators, who demonstrated the normal range of total blood volume to be 66 to 88 ml. per kg. At this hospital, on the basis of investigations of normal subjects, the following range has been established:

Red-cell mass: 28–35 ml. per kg.
Plasma volume: 40–50 ml. per kg.
Total blood volume: 68–85 ml. per kg.

The results obtained before treatment in 35 patients are shown in Table II. The values for red-cell mass ranged from 30 to 92 ml. per kg. Berlin, Lawrence, and Gartland (1950) found that in 30 patients with polycythaemia the red-cell mass varied between 38·8 and 93·9 ml. per kg. Only one of our patients had a red-cell mass within normal limits. Measurements in his case were made shortly after a severe gastrointestinal haemorrhage. The Table does not include blood-volume estimations performed in some of the earlier patients by means of ^{32}P-labelled erythrocytes (Reeve and Veall, 1949), the results of which have already been reported by Abbatt, Chaplin, Darte, and Pitney (1954). In 90 per cent. of the patients the total blood volume was increased. This was primarily due to the increase in the red-cell mass, occasionally augmented by the increased plasma volume. Half of the patients studied had a blood volume greater than 100 ml. per kg. body weight, ranging to as high a figure as 140 ml. per kg.

It is important to realize that there is not a good correlation between the packed-cell volume and the red-cell mass. The plasma volume was within

normal limits in only 15 of the 35 patients. In the others it was either decreased or increased for a given red-cell mass. As a result of this variation the real extent of the polycythaemia is not reflected by the values for packed-cell volume. In this connexion it is interesting to note that a pseudo-polycythaemic condition has been described (Lawrence, 1955) in which hypertension, obesity, and mental

TABLE II

Blood-volume Measurements in 35 Patients, estimated by the ^{51}Cr Method

Patient	*Red-cell mass (ml. per kg.)*	*Plasma volume (ml. per kg.)*	*Total blood volume (ml. per kg.)*	*Packed-cell volume (%)*
A. W.	30	78	108	51
M. K.	36	37	73	61
J. H.	37	34	71	57
E. C.	39	30	69	62
C. B.	39	44	83	52
D. A.	40	43	83	53
E. D.	40	36	76	58
L. H.	42	34	76	64
C. W.	42	35	77	61
E. B.	44	35	79	62
G. D.	45	41	86	56
A. B.	48	46	94	59
F. K.	51	19	70	70
E. L.	51	30	81	72
B. B.	53	41	94	63
M. T.	53	45	98	62
J. T.	55	37	92	69
F. A.	58	44	102	62
M. E.	59	62	121	62
B. N.	60	43	103	64
J. S.	63	32	95	73
M. R.	63	25	88	64
L. W.	64	44	108	63
A. S.	72	46	118	71
M. M.	72	38	110	74
K. H.	73	43	116	73
B. P.	73	35	108	76
W. W.	75	37	112	74
J. B.	75	52	127	69
R. A.	76	34	110	75
F. W.	76	46	122	72
G. D.	78	41	119	74
B. M.	83	60	143	64
E. R.	85	45	130	70
C. K.	92	48	140	74

stress are associated with haemoconcentration, although the red-cell mass is normal. In contrast to this syndrome, which has been termed stress polycythaemia, a condition of increased plasma volume is sometimes found, usually in association with cirrhosis of the liver (Loge, Lange, and Moore, 1958); the packed-cell volume would suggest an anaemia, but here again the red-cell mass is normal. It is clear, therefore, that estimations of red-cell volume are of great value, and sometimes essential for establishing the diagnosis and severity of the disease.

Red-cell count. The upper limit of normal in the present series has been taken as 6,000,000 per cu. mm. in men and 5,500,000 per cu. mm. in women (Dacie,

1956). It must be remembered, however, that occasionally the severity of the disease is obscured by a recent haemorrhage or venesection, or by previous treatment by irradiation. Fig. 2 shows the erythrocyte levels in our patients at the time of their first treatment. Eight patients had counts below the upper limit of normal; the dominating feature in these patients was recent loss of blood.

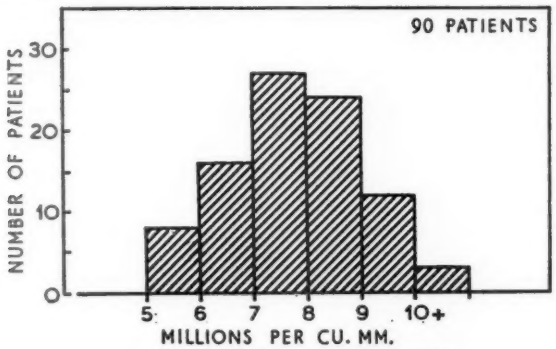

FIG. 2. Range of red-cell counts.

Although in polycythaemia there is a marked increase of erythrocyte production, reticulocytosis is not a common feature. The reticulocyte values in the present series were as follows:

Less than 2 per cent.	54 per cent. of cases.
2 to 3 per cent.	32 per cent. of cases.
3 to 4 per cent.	9 per cent. of cases.
4 to 5 per cent.	5 per cent. of cases.

Several of the patients with a significant reticulocytosis gave a history of recent haemorrhage. In polycythaemia, therefore, there does not appear to be any defect in the late stages of maturation and the release of erythrocytes from the marrow. There has been some uncertainty about the erythrocyte survival in polycythaemia vera. London, Shemin, West, and Rittenberg (1949) found a normal life span, using ^{15}N glycine. Similar results were noted by Ranney (1958). On the other hand Berlin, Lawrence, and Lee (1951), using ^{14}C, obtained results which they thought could be explained by the presence of two cell populations, one with a shortened and the other with a normal life span. Lawrence (1955) considered that an analysis of iron-turnover values in polycythaemia vera confirmed this deduction. The cell survival has been studied in six of our patients by the ^{51}Cr method; the results were within normal limits, and in all cases approximately half the chromium was still present in the circulation on the 26th day.

Haemoglobin. The upper level of normal haemoglobin values has been taken as 16·5 g. per 100 ml. in men and 15·5 g. per 100 ml. in women (Dacie, 1956). The following results were obtained in the 90 patients:

Haemoglobin less than 14·8 g. per 100 ml.	10	patients
14·8 to 17 g. per 100 ml.	17	,,
more than 17 g. per 100 ml.	63	,,

As in the case of the erythrocyte counts, the 10 patients in whom the haemoglobin content was less than 14·8 g. included nine who had a clear-cut history of recent haemorrhage or venesection. It will be seen that the haemoglobin was increased in the majority of cases, but the increase was not closely parallel to the erythrocytosis, since many cases were associated with chronic loss of blood. This loss resulted in an iron deficiency, and the erythrocytes, although increased in number, were hypochromic and microcytic. The mean corpuscular haemoglobin concentration was less than normal in 78 per cent. of the patients.

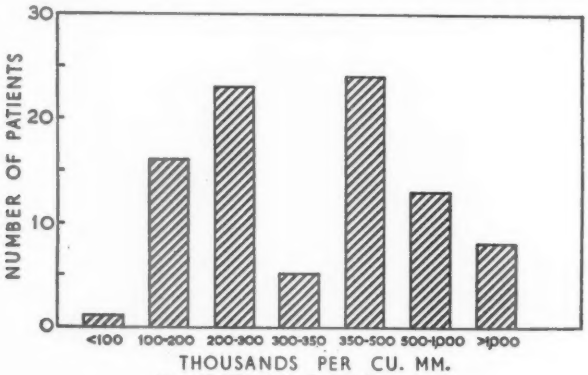

FIG. 3. Range of platelet counts.

Leucocytes. The total leucocyte count was raised above the upper level of normal (10,000 per cu. mm.) in 71 per cent. of the patients: in 14·5 per cent. it was above 25,000. The leucocytosis was frequently associated with a shift of the neutrophils to the left. In the remaining 29 per cent. the leucocyte counts were within the normal range (4,000 to 10,000 per cu. mm.), and in no instance was there a leucopenia. These findings are similar to those of Lucas (1912) and Lawrence (1955), in 67·7 per cent. and 74 per cent. of whose patients respectively there was leucocytosis. In 24 per cent. of our cases myelocytes were seen, but they did not comprise more than 1 per cent. to 2 per cent. of the total leucocyte count. This proportion of cases is less than that reported by Lawrence (1955), who gave a figure of 70 per cent. of 159 patients. Blast cells were not found in any of the uncomplicated cases.

Platelets. In this hospital the normal range of platelets in the peripheral blood has been taken to be 100,000 to 350,000 per cu. mm. Although thrombocytosis is considered to be a usual feature of polycythaemia vera (Dameshek, 1936; Wintrobe, 1956), only about half the patients in our series had a significant increase in platelets; it occurred less frequently than leucocytosis (Fig. 3). The significance of these findings in relation to diagnosis is discussed later. In some patients the increase in platelets seems to be the dominating feature both clinically and haematologically. Some authors have recognized as a separate entity a condition described by such names as primary, essential, or haemorrhagic thrombocythaemia (Rowlands and Vaizey, 1938; Reid, 1940; Fanger, Cella, and Litchman, 1954). Eight of our patients had initial platelet counts in

excess of 1,000,000 per cu. mm., and might be considered to belong to this group. The presenting symptoms and essential haematological data in these patients are shown in Table III. Haemorrhagic and thrombotic incidents were extremely frequent. It will be noted that all patients had high leucocyte counts, and in all except one there was erythrocytosis. Thus there appears to be no reason to separate this group from polycythaemia vera, of which 'essential thrombocythaemia' seems to be a variant. The following case history illustrates the clinical and haematological course of 'essential thrombocythaemia' in a patient who showed an extreme form of the condition.

TABLE III

Haematological Features and Vascular Complications in Patients with 'Essential Thrombocythaemia' before Treatment with ^{32}P

Patient	*Red cells (millions/ cu. mm.)*	*White cells (thousands/ cu. mm.)*	*Neutrophils (thousands/ cu. mm.)*	*Platelets (thousands/ cu. mm.)*	*Thrombosis*	*Haemorrhage*
G. B.	7·3–9·6	76	73*	1,600–2,000	—	+
E. D.	6·0–8·2	39	30	1,000–1,600	+	—
A. G.	6·2–6·6	40	34	1,000–1,200	+	+
E. H.	8·0–8·2	14	12	1,100–1,260	—	—
A. L.	4·3–5·2	50	45*	2,500–4,000	+	+
L. M.	6·0–6·2	14	13	1,000–1,800	+	+
J. P.	6·3	40	33	1,800	+	+
A. S.	6·4–7·1	37	30	1,500	+	+

* Myelocytes in peripheral blood.

Patient A. L. (Fig. 4) was aged 58 when first seen at Hammersmith Hospital in September 1953. In 1950 he developed weakness, dyspnoea, anginal pain, and pain in the fingers and toes. He was found to be anaemic by his private doctor, and was treated for some time with vitamin B_{12}, with some improvement.

In April 1952 he was admitted to hospital with gastrointestinal haemorrhage; a barium meal revealed a large gastric ulcer. In July 1953 he was readmitted after further attacks of gastrointestinal bleeding; a partial gastrectomy was performed. A blood count revealed thrombocytosis and leucocytosis. A bone-marrow examination showed excess of megakaryocytes. He was then transferred to Hammersmith Hospital for further investigations.

On admission he was found to have a red-cell count of 5,100,000 per cu. mm., haemoglobin 12·9 g. per 100 ml., white cells 39,000 per cu. mm., and platelet counts which fluctuated between 2,500,000 and 4,000,000 per cu. mm. The liver was found to be enlarged to 5 cm. below the costal margin, but the spleen was not palpable. It is interesting to note that the spleen has remained impalpable up to September 1958, when he was last seen, and that it appeared normal at operation. A bone-marrow examination again showed abundant fragments packed with cells, and a great increase in the number of megakaryocytes; no free iron was present. Shortly after admission the patient had further gastrointestinal haemorrhages, and became jaundiced. It was considered that the jaundice was due to serum hepatitis. During his recovery from jaundice gastrointestinal haemorrhages persisted, although the results of radiological investigation were normal. The haemorrhagic diathesis was believed to be due to the thrombocythaemia. On 30.12.53 he was given 5 mc of ^{32}P intravenously, at a time when his platelet count was over 4,000,000 per cu. mm. After this his condition improved, and he was discharged towards the end of January. In April 1954 his red-cell count was 5,000,000 per cu. mm., haemoglobin 10·5 g.

per 100 ml., white cells 29,000 per cu. mm., and platelets 1,500,000 per cu. mm. His condition deteriorated during the following two months, and on 1.7.54 he was given 6 mc of ^{32}P. The platelet count, from 2,800,000 per cu. mm., again fell to approximately 1,250,000 per cu. mm.

He remained fairly well until March 1955, when he developed thrombophlebitis in the left leg. In April 1955 a further 6·25 mc of ^{32}P was given, after which the platelet count fell to 560,000 per cu. mm. The number of platelets again rapidly increased, and he had further thrombophlebitis, involving the

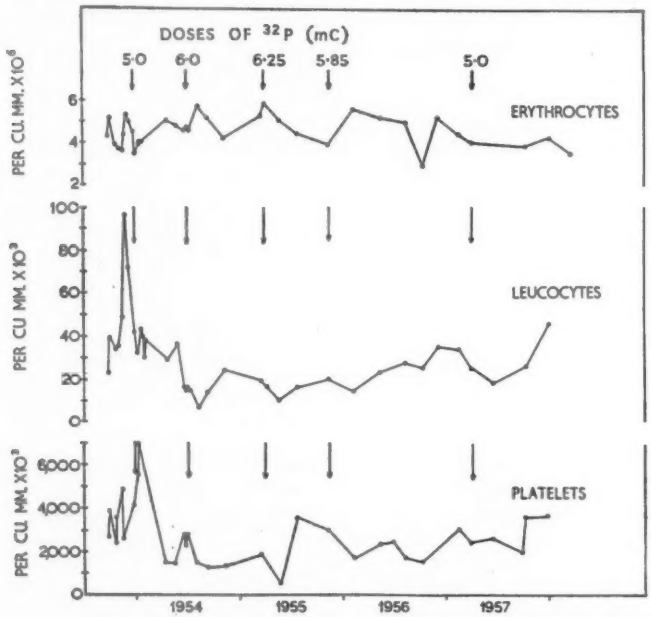

FIG. 4. Haematological data and response to treatment with ^{32}P in a patient (A. L.) with 'essential thrombocythaemia'.

veins of the right leg; he was again admitted to hospital, and given 5·85 mc of ^{32}P on 7.11.55. The fall in the platelet count was transitory, and by July 1956 the count had risen to the level observed before treatment. His general condition, however, improved, and he remained well, without any further haemorrhagic or thrombotic episodes, for about a year. In December 1956 he was admitted to his local hospital with acute epigastric pain and vomiting. At laparotomy multiple adhesions were found and divided. He made a good recovery. In February 1957 his platelet count was over 3,000,000 per cu. mm., and in April 1957 he was given 5 mc of ^{32}P. Since that time he has had no recurrence of haemorrhagic or thrombotic incidents. His most recent blood count showed red cells 4,000,000 per cu. mm., haemoglobin 8·9 g. per 100 ml., white cells 26,000 per cu. mm., and platelets 3,500,000 per cu. mm.

A. L. differed in several respects from the other seven patients who had platelet counts of over 1,000,000 per cu. mm. His red-cell count has never been above 5,300,000 per cu. mm. There were frequent episodes of bleeding, and he has always been deficient in iron. The platelet count was considerably higher

than that of any other patient. It was never reduced to normal limits, and was only on one occasion below 1,000,000 per cu. mm.

Patients with normal white-cell and platelet counts. The occurrence of normal leucocyte or platelet counts has been noted in many reviews (Lucas, 1912; Wiseman, Rohn, Bouroncle, and Myers, 1951; Lawrence, 1955; Fountain, 1957;

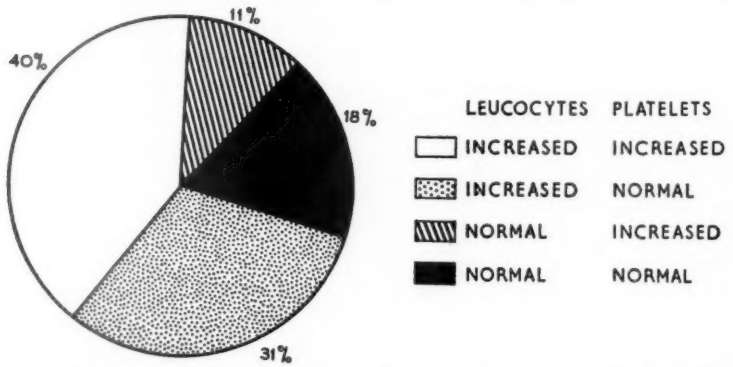

FIG. 5. The incidence of leucocytosis and thrombocytosis in polycythaemia vera.

TABLE IV

Haematological and Clinical Features of Patients with Polycythaemia Vera in whom both Leucocyte and Platelet Counts were Normal before Treatment with ^{32}P

Patient	*Red cells (millions/ cu. mm.)*	*White cells (thousands/ cu. mm.)*	*Neutrophils (thousands/ cu. mm.)*	*Platelets (thousands/ cu. mm.)*	*Spleno-megaly*	*Hepato-megaly*
R. A.	8·2	5	3·0	270	—	—
F. A.	7·6	7	5·0	108	+	+
A. A.*	9·3	6–8	4·8–7·0	130–230	+	+
J. B.	7·2	7–8	4·0–5·0	150–260	+	+
L. C.	7·1	9	6·0	330	+	—
E. C.	7·8	6–7	4·0–5·8	90–120	+	+
W. C.	9·3	8	5·5	270	+	+
J. F.	8·4	9	7·0	160	+	+
Y. G.*	9·0	8	6·8	150	+	+
S. K.*	8·4	10	6·0–7·7	100–120	+	—
W. K.	7·9	7–9	5·0–6·5	60–100	?	+
L. P.	8·0	5–8	4·5–6·5	220–240	+	—
E. R.*	6·0	9	7·5†	250	+	?
J. S.	7·8	4–5	2·5–2·7	200–250	—	—
A. S.	8·4	5–9	3·5–8·0†	150–250	+	—
H. T.	5·6	4–6	2·5–3·8	126–250	+	+

* Previously treated by irradiation.
† Myelocytes in peripheral blood.

Verel, 1958). None of the reports, however, give the number of patients in whom both leucocyte and platelet counts were normal. This finding has not been sufficiently recognized, so that many clinicians are reluctant to diagnose polycythaemia vera in the presence of normal leucocyte and platelet counts, even when secondary polycythaemia has been excluded by thorough investigation. Sixteen of our patients had leucocyte and platelet counts which were consistently below the upper limits of normal (Fig. 5). Only four had previous

treatment by radiation. The degree of erythrocytosis varied, and was considerable in several of the patients (Table IV). The subsequent clinical and haematological findings and response to therapy in these patients were similar to those observed in the other patients of the present series (Fig. 6).

Marrow findings. The characteristic features of polycythaemia vera have usually been described as follows. There is crowding of cellular elements, with loss of fat-spaces; granulopoiesis and erythropoiesis are increased, with a relatively greater degree of the latter, sometimes resulting in a reversal of the

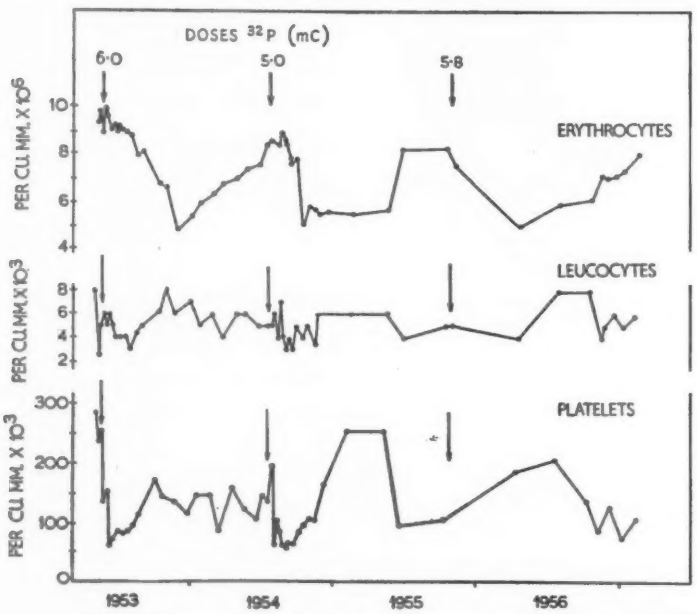

FIG. 6. Haematological data and response to treatment with ^{32}P in a polycythaemic patient with normal leucocyte and platelet counts.

myeloid:erythroid ratio. Erythropoiesis is normoblastic, and there are macronormoblasts, but no megaloblasts are seen, and megakaryocytes are increased in number. This classical picture, however, was found in only one-third of our cases (Plate 27, Fig. 11). The commonest characteristic feature observed was loss of fat-spaces, and this gave an approximate indication of the degree of erythrocytosis in the peripheral blood. The myeloid:erythroid ratio was reduced below the lower limit of normal (1:2·5) in 70 per cent. of cases; in one-third of the latter group the ratio was reversed. The number of megakaryocytes seen in a smear depends largely on the technique of preparation, and it is therefore difficult to attach any quantitative significance to examination of the smear. In about half the cases, however, the number of megakaryocytes was obviously increased. Depletion of iron stores was a feature in 80 per cent. of the marrow specimens, and in the majority no free iron was seen. The marrow was normal

in 18 per cent. In about half the cases only some of the characteristic features were present, and it was not possible to make a firm diagnosis from the morphological appearance. Examination of the marrow of the patients with normal leucocyte and platelet counts did not reveal any significant difference from the series as a whole. In some there appeared to be increased granulopoietic and thrombopoietic activity in spite of the peripheral blood values. In the group of patients with thrombocythaemia cellular crowding of the fragments, with loss of fat-spaces, was a common finding; numerous megakaryocytes, which appeared morphologically normal, were present. The myeloid:erythroid ratio was within normal limits in all but one patient of this group; iron stores were depleted in all cases.

Marrow changes are more readily detected in bone biopsy material, in which a characteristic histological picture may be seen. The value of bone biopsy has also been noted by Block and Bethard (1952). Our sections showed the following features: loss of fatty tissue; increased cell infiltration, with preponderance of the erythroid series, and numerous megakaryocytes at all stages of development (Plate 27, Fig. 12). The presence of increased reticulin material is suggestive of myelosclerosis, and the onset of this condition can be detected at an early stage by the characteristic histological appearance of diffuse fibrosis (Plate 28, Fig. 13).

TABLE V

Incidence of Haemorrhage and Thrombosis in relation to the Platelet Count

		Platelets	
	Total	*100,000–350,000 per cu. mm.*	*Above 350,000 per cu. mm.*
Haemorrhage:			
Gastrointestinal	15	3	12
Subcutaneous	10	2	8
Haematuria	5	3	2
Haemoptysis	2	1	1
Other sites (nose, eyes, teeth, &c.)	16	9	7
Thrombosis:			
Cardiac	7	3	4
Leg	15	2	13
Other sites	4	2	2
**Cerebro-vascular episodes*	9	8	1

* It is impossible to say whether the cerebral episodes were due to haemorrhage or thrombosis.

Thrombosis and haemorrhage. Thrombotic and haemorrhagic episodes occur commonly during the course of the disease. Table V illustrates the frequency with which they occurred in our series. In the case of cerebro-vascular accidents it is usually impossible to distinguish clinically between thrombosis and haemorrhage, and they have therefore been placed in one group. These complications have been analysed according to site, but it must be realized that more than one incident may occur in a single patient. Both haemorrhage and thrombosis

may occur in the same patient at different times, and may be associated with normal or high platelet counts; some of the worst episodes of haemorrhage have occurred in the group with thrombocythaemia. Table V also shows the relationship of haemorrhage and thrombosis to the platelet count. In view of the small numbers in each group it is difficult to draw any definite conclusion, but it will be seen that gastrointestinal haemorrhage and leg thrombosis occurred more frequently in patients with high platelet counts, whereas cerebro-vascular accidents were usually associated with normal platelet counts. We have not, however, been able to show an overall statistical correlation between a high platelet count and a tendency to haemorrhage or thrombosis. The majority of patients with polycythaemia vera appear to have an increased tendency to haemorrhage, and even routine venepuncture seems to occasion prolonged oozing from the puncture site. The increased blood volume, with defective vessel retraction because of venous engorgement and capillary distension, may be partly responsible. Björkman (1948) reported the occurrence of fibrinogenopenia in polycythaemia vera. This was confirmed by Stefanini, Chatterjea, and Dameshek (1954), who demonstrated that the fibrinogen level could be increased to within normal values as a result of treatment with ^{32}P or some other method. It is not clear why patients with a marked increase in platelets should have frequent haemorrhagic episodes. Rosenthal (1949) was able to demonstrate defective clot retraction, but this finding has not been confirmed by other workers (Henstell, Henstell, and Ornitz, 1951). Biggs and Macfarlane (1957) were unable to demonstrate a coagulation defect in polycythaemia vera. Hardisty and Wolff (1955) studied five patients with 'haemorrhagic thrombocythaemia', and found that the platelets were qualitatively different, judged by their behaviour in the thromboplastin-generation test. The coagulation mechanism was studied in our patient A. L., described above. No deficiency of any coagulation factors was observed, but the thromboplastin-generation test showed an abnormality which appeared to be due to an inhibitory action of the excessive numbers of platelets, and this was corrected when the platelets were diluted to an equivalent of 300,000 per cu. mm. (Pitney, 1955).

Treatment of Polycythaemia Vera

As the underlying cause of polycythaemia vera is unknown, treatment has aimed at the reduction of blood volume and depression of the increased marrow activity. The numerous methods used in the past indicate that none has been entirely satisfactory or produced sufficiently long remissions.

Venesection is still commonly used, and is considered by some to be the treatment of choice (Dameshek, 1950). It has the advantages that it often produces rapid symptomatic relief and prevents the excessive accumulation of breakdown products of cell metabolism. It is not, however, satisfactory as a routine method. In many cases the effect is transient; in others, after a period of initial apparent benefit, venesection seems to have less and less clinical effect, and leads to serious iron deficiency. Furthermore, loss of blood stimulates marrow

activity, and venesection does not alter the fundamental abnormality of the disease. Venesection, however, has a place in the treatment of polycythaemia in certain circumstances: (1) When rapid reduction in blood volume is necessary before, for example, emergency surgical operations, or when the clinical picture suggests an impending vascular catastrophe. (2) In young patients, in whom the disease is mild, and to whom it is undesirable to administer high doses of radiation. (3) In patients who fail to show a satisfactory response to adequate ^{32}P therapy.

Diet. In order to eliminate haemopoietic substances, special iron- and protein-deficient diets have been devised. No clear evidence has been produced to indicate that they are of significant value. Their preparation is complicated, and it is difficult to maintain patients on such a diet.

Chemotherapy. Since the disease was first recognized, chemical agents have been used either as marrow depressants or as haemolytic substances. One of the first used was arsenic, the classical therapeutic stand-by of the early twentieth century. Benzol and similar substances were also tried. Phenylhydrazine has been the most popularly used drug for inducing haemolysis, and for many years it was the treatment of choice; but its effect was difficult to control, and it could produce so severe a degree of haemolytic anaemia that transfusions were required. Four of our patients were treated earlier with phenylhydrazine; two finally required blood transfusions. Other disadvantages of the drug are the toxic effects on the liver and the fact that it is considered to increase the liability to thrombosis. Even protagonists of this method advised against its use in patients who are liable to thrombosis (Giffin and Conner, 1929). Since the Second World War alkylating agents, such as nitrogen mustard and its analogues, have been used in polycythaemia, in view of their known effect in depressing the marrow. Wilkinson and Fletcher (1947) and Woodruff (1948) found the nitrogen mustards of little value in a small group of patients; Spurr, Smith, Block, and Jacobson (1950) reported an average remission of 6·5 months. Triethylene melamine has been a popular remedy, especially in the United States (Rosenthal and Rosenthal, 1952; Ellison, Ginsberg, and Watson, 1953; Wasserman, 1954). Rosenthal and Rosenthal reported an average remission of eight to nine months. On the whole, chemotherapy has not proved sufficiently reliable in producing remissions, and when produced they are of comparatively short duration. The side-effects of the treatment can at times be very distressing to the patient.

Irradiation has been used in the treatment of polycythaemia vera for at least 40 years. Various radiotherapeutic techniques have been employed: (1) Splenic irradiation; this has never been effective. (2) Irradiation of bones which contain red marrow; laborious techniques were devised, but treatment was most commonly directed to the long bones and spine (Pack and Craver, 1930; Windeyer and Stewart, 1952). (3) Total body irradiation. Before the introduction of radioactive phosphorus this was probably the most frequently used method (Pierson and Smith, 1940; Richardson and Robbins, 1948; Paterson, 1948). At first some workers were not impressed by the results of irradiation, as their

assessments of response were based on the blood findings shortly after treatment, and it was not realized that the red-cell count decreases much later than the leucocyte and platelet counts. Remissions have been obtained, but large doses to the bones over a period of weeks are required, and total body irradiation is likely to induce radiation sickness.

Radioactive phosphorus. A notable advance in the management of polycythaemia vera was the introduction of ^{32}P by Lawrence and his associates in 1938 (Lawrence, 1940). This isotope of phosphorus is a pure β-ray emitter, and has a physical half-life of 14·3 days. The electrons produced have an energy of 1·7 mev., with a maximum penetration in soft tissues of 8 mm. and a half-path of about 2 mm. ^{32}P is supplied as the dibasic sodium salt, and can be given either intravenously or orally. When given orally, about 25 per cent. is not absorbed from the gastrointestinal tract and is excreted in the faeces. This figure, however, may vary considerably from patient to patient and, as the dosimetry of phosphorus therapy already depends on a number of unknown variables (see below) the majority of workers prefer the intravenous route. Satisfactory results can, however, be obtained with ^{32}P given orally (Wiseman, Rohn, Bouroncle, and Myers, 1951), and additional exposure of personnel to radiation is thereby avoided. When used orally the dose is increased by a factor of $\frac{4}{3}$ in order to compensate for the 25 per cent. that will not be absorbed from the gastrointestinal tract.

The uptake of ^{32}P in a tissue depends on (1) the total amount of phosphorus in exchangeable form in the tissue, (2) the rate of turnover of phosphorus by the tissue, and (3) the rate at which new tissue is being formed (Reinhard, Moore, Bierbaum, and Moore, 1946). The greatest uptake is therefore found to be in bone-marrow, liver, spleen, and neoplastic tissue. Low-Beer, Blais, and Scofield (1952), in an attempt to estimate dosage for intravenously administered ^{32}P, found it useful to divide the body into two compartments: (*a*) bone, spleen, and liver, and (*b*) the other soft tissues. On the basis of experimental data they assumed that after a three-day period of equilibration the ratio of concentration in *a* to that in *b* is 10:1. The dose ratio between the two compartments, taking into account the first three days, is 9:1. Recently some doubt has been thrown on the value of this ratio, which may be very much lower (Wyard, 1956). Further information as to the distribution of ^{32}P in bone is clearly needed. The total body irradiation from ^{32}P has been estimated by Brues (1949), who stated that 1 mc given to a man of 60 kg. yields an integrated dose of about 15 rep. (roentgen equivalents physical) at a rate of less than 1 rep. per day; this does not take into account loss by excretion. The biological half-life of ^{32}P has been estimated to be eight days (Tivey and Osgood, 1950).

Dosimetry. In addition to the physical characteristics and differential absorption ratios mentioned above, the dosimetry of ^{32}P therapy depends on the proportion of the administered dose retained in the body, and on the amount of erythropoietic tissue present in the individual patient receiving treatment. 1. *Urinary excretion.* The fraction of the dose excreted in the urine varies considerably from patient to patient, and in the same patient at different times.

Data regarding the urinary excretion of ^{32}P have been obtained after 153 injections. The mean value for the amount excreted in the first 48 hours was found to be $10{\cdot}4 \pm 4{\cdot}3$ per cent., but the range was from 3 per cent. to 30·7 per cent. Fig. 7 shows a typical excretion curve. 2. *Erythropoietic tissue.* Although the amount of red marrow in a normal person has been calculated, it is not possible with the methods at present available to estimate the quantity of erythropoietic tissue present in a given patient with polycythaemia. Surface counting methods using ^{32}P, or tracer doses of ^{59}Fe, are of little value. A knowledge of the amount of erythropoietic tissue which is being irradiated is obviously of great importance in any attempt at estimating dosage.

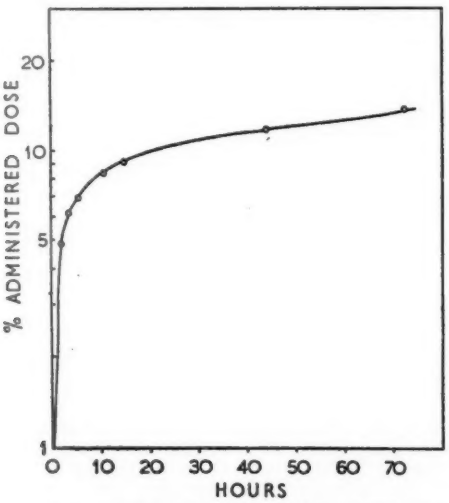

FIG. 7. The urinary excretion of ^{32}P after a therapeutic dose.

Dosage. Because of inadequate knowledge of the dosimetry of ^{32}P in polycythaemia vera, methods of estimating a therapeutic dose are largely empirical. Even if the problem of dosimetry were solved, there would remain the additional and important problem of the difference in individual sensitivity of patients to irradiation, a factor which has been observed by radiotherapists in the treatment of other types of malignant disease. Various schemes of treat ment have been suggested. They are, in general, related to the weight of the patient (Osgood, 1956), the height of the initial red-cell count (Wiseman, Rohn, Bouroncle, and Myers, 1951), or the magnitude of the red-cell volume (Verel, 1958), or to a combination of these factors. Many workers attempt to reduce the red-cell mass to normal levels by venesection before embarking on ^{32}P therapy. When treatment with radioactive phosphorus was begun at Hammersmith Hospital, the following technique was used for about a year. Two doses of approximately 3·5 mc of ^{32}P were given by intravenous injection at an interval of 10 to 14 days. Each injection was preceded by venesection at which from one

to two pints of blood were removed. No special advantage was noted in the use of this method and, as it had certain drawbacks, including two admissions of the patient to hospital, it was abandoned in favour of a single injection. The dose given to patients at present varies between 4 and 7 mc. Heavy patients with a high red-cell mass are given 6 to 7 mc; lighter patients with a lower red-cell mass are given 4 to 5·5 mc. The dose given to our patients is higher than that usually reported, and may account for a longer average period of remission in the present series. Venesection before treatment with ^{32}P is not a routine procedure, and is employed only when a vascular catastrophe appears to be threatening. Patients remain in hospital for a period of 48 to 72 hours after an injection; by this time the urinary excretion has reached a safe level (less than 100 μc in 24 hours).

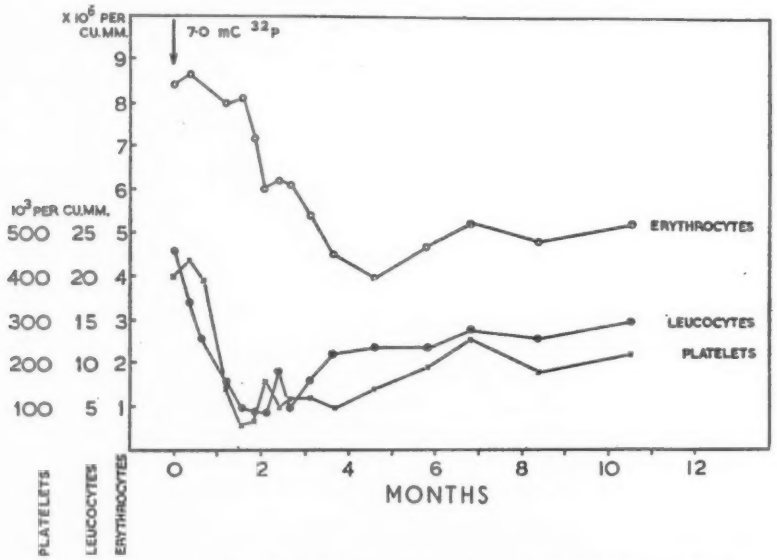

FIG. 8. Satisfactory response to a single injection of ^{32}P.

Effects of ^{32}P treatment. As a general rule the first effect of the ^{32}P therapy is on the platelets (Fig. 8). It is not usually obvious for about three weeks, and the lowest levels are not reached until 30 to 50 days. Abbatt, Chaplin, Darte, and Pitney (1954) found that there was a correlation between the degree of platelet depression and the ultimate clinical response. The fall in the white-cell count frequently parallels that of the platelets, but is more variable. There is also an alteration in the differential count, and the granulocytes in the peripheral stream become more mature. A significant depression of the erythrocyte level does not usually occur in less than six to eight weeks, and occasionally does not become apparent for three or four months. This delay in response may be explained by the comparatively long life span of erythrocytes (100 to 120 days), and by the fact that ^{32}P is believed to act on the early red-cell precursors

in the marrow. The above findings stress the point made by many observers, that with such a scheme of treatment further ^{32}P should not be given until an interval of at least four months has elapsed.

After discharge from hospital, patients are seen four weeks later for a full clinical and haematological assessment. When a remission has been achieved, the patient is seen at two- to three-monthly intervals. A symptomatic response usually occurs before any haematological changes are apparent, but it is difficult to understand why this is so. Repeated satisfactory clinical and haematological remissions can be obtained (Fig. 9). The aim of the treatment is to induce a clinical and haematological remission. If after four months from the initial injection this object has not been achieved, a further injection is given. The question of re-treating a patient who relapses should be decided after consideration of both the clinical and the haematological status. Difficulty occasionally arises in patients who remain free of symptoms but have relapsed haematologically. In general our policy is to maintain the blood picture within normal limits, in order to prevent as far as possible the complications of thrombosis and haemorrhage. The criteria for dosage when the patient is re-treated are the same as for the initial treatment, but the original response is taken into consideration.

Results

The results of the initial course of treatment can be evaluated in 78 patients treated before January 1, 1957, whose progress has been followed for at least one year. The response to treatment has been evaluated as follows:

1. *Full remission*: disappearance of all reversible symptoms, and a return of the blood picture to within normal limits, for at least six months.
2. *Partial remission*: disappearance of all reversible symptoms, or a return of the blood picture to within normal limits.
3. *No remission*: failure to induce either a symptomatic or a haematological remission.

Analysed in this way, 64 patients (82 per cent.) had a full remission; 10 patients (13 per cent.) had a partial remission; three patients (4 per cent.) had no remission; and one patient could not be assessed. (This patient was a seaman, who returned to his ship, and died at sea seven months later apparently from a myocardial infarction.) Of the 64 patients who had a full remission, 44 required one injection, 19 two injections, and one three injections to achieve this end. These injections were given at intervals of less than six months. For purposes of the present analysis they were considered to constitute a single course, since the effect on erythropoiesis is assumed to be due to summation of all the administered ^{32}P.

In the present series the average period of remission has been 22·3 months. This figure is almost certainly an under-estimate, since patients still in remission were included in calculation of the average. The length of a remission varied considerably from one patient to another, and the range has been from six to

80 months. When the duration of the first remission is compared with that of subsequent remissions in the same patient, it is striking how frequently they are

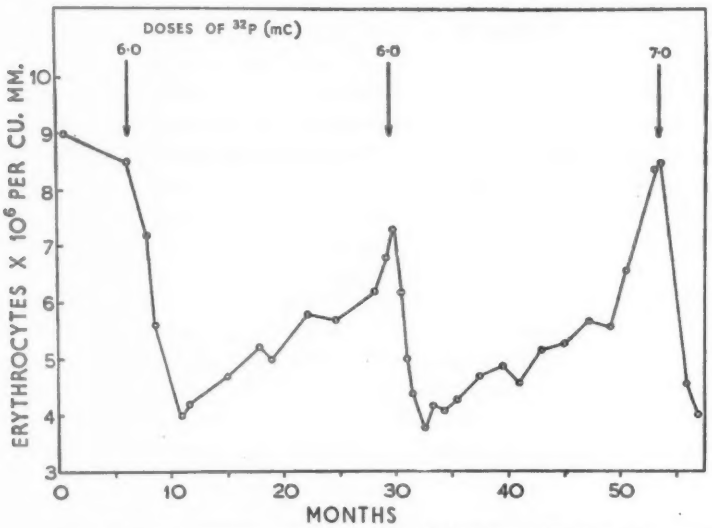

FIG. 9. Erythrocyte response to repeated injections of ^{32}P. It will be noted that the disease does not appear to be quiescent in the intervals between treatment (cf. Fig. 10).

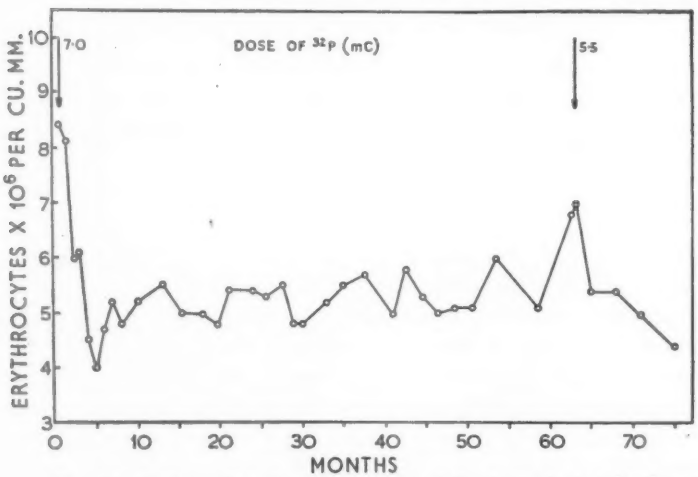

FIG. 10. Prolonged erythrocyte response following a single injection of ^{32}P. There appears to be a quiescent phase in this patient (cf. Fig. 9).

of similar or even identical duration. The response in polycythaemia to treatment with ^{32}P appears to differ in this respect from the response to radiation therapy of chronic leukaemia, in which the periods of remission tend to become progressively shorter and ultimately the disease becomes almost completely

resistant to treatment. When the erythrocyte counts are charted, it becomes apparent that in many patients the disease is never really quiescent (Fig. 9). After falling to a certain level the counts show a continuous and progressive rise. In other patients there appears to be a prolonged period of remission during which the erythrocytes remain at a more or less constant level (Fig. 10). No relationship has been found between the duration of the remission and the initial magnitude of the red-cell mass or total blood volume. The presence of myelocytes in the peripheral blood before treatment does not appear to affect the nature or duration of the remission. When a full remission is obtained, the red-cell mass returns to normal. As a general rule the effect of treatment on the plasma volume is to cause a return towards normal values: if it was previously increased it diminishes, and vice versa. Abbatt, Chaplin, Darte, and Pitney (1954) made a detailed study of the platelet response following treatment with ^{32}P, and found that a fall of the platelet count below 100,000 usually resulted in a remission; they suggested that there was a correlation between the platelet response and the clinical result. We have compared the platelet count at one month in patients who had a full haematological remission and in those without such a remission; lower values were found in the first group than in the second. There were, however, many exceptions, and it is felt that the initial platelet response does not necessarily provide a prognostic criterion on the basis of which ^{32}P therapy can be repeated earlier. No correlation was found between the white-cell count at one month and the clinical response. It is our general policy to wait for at least three to four months before giving further treatment. The red-cell count fell to 3,500,000 per cu. mm., or less, in only four patients. The white-cell count was depressed to below 4,000 per cu. mm. in only five, but the platelet count was depressed to 100,000 per cu. mm., or less, in 35 patients. ^{32}P therapy did not produce in any of the patients pancytopenia, with a concomitant depression of all the blood elements below the levels mentioned above.

Causes of death. The commonest causes of death of untreated patients, or of patients treated before the introduction of ^{32}P, were haemorrhage and thrombosis. The other causes were congestive cardiac failure, carcinoma, leukaemia, and intercurrent infections. In the present series 19 patients have died. Necropsy examinations were performed in 13. The causes of death have been analysed as follows:

Cerebral haemorrhage or thrombosis	4
Myocardial infarction	3
Carcinoma of bronchus	3
Leukaemia	2
Myelosclerosis	1
Carcinoma of kidney	1
Myelomatosis	1
Cirrhosis of liver	1
Abdominal tuberculosis and gastric ulcer	1
Suicide	1
Cerebral degeneration following previous cerebro-vascular accident	1

It will be noted that seven patients died from haemorrhage or thrombosis.

In none of the reported series have these complications been completely abolished, but it is possible that with more careful control the incidence might have been further reduced. The association of polycythaemia vera and cirrhosis is well recognized and, in fact, has been deemed worthy by some of a separate name—Mosse's syndrome. The pathogenesis is not clearly understood (Mosse, 1914). An interesting development reported is the occurrence of primary splenic tuberculosis in polycythaemia vera (Wintrobe, 1956). One of our patients was found at post-mortem examination to have this complication. Another patient died from multiple myelomatosis. The association of these two diseases has been commented on in some reports, and it has been suggested that it is an expression of their common origin from the same primitive multipotential cell (Lawrence and Rosenthal, 1949; Giertsen, 1956).

Leukaemia in Polycythaemia

There have been many reports of the association of polycythaemia vera and leukaemia. The majority of patients showing this association have had previous irradiation, but several well authenticated cases have been reported in which leukaemia has developed in patients who have had no previous treatment (Dameshek, 1950). It is impossible to establish the true incidence of leukaemia in non-irradiated patients. Schwartz and Ehrlich (1950) found only one unequivocal case in a critical assessment of 83 reported cases. It is obviously difficult, in retrospect, to decide whether patients who were thought to have leukaemia did in fact have this complication, or merely the leukaemoid reaction which so commonly occurs in polycythaemia or myelosclerosis. As already mentioned, there is evidence that polycythaemia vera is a member of the myeloproliferative group of diseases, and if this is so the development of leukaemia might be expected. Recent work has suggested biochemical differences in the leucocytes of leukaemia and polycythaemia. Valentine, Beck, Follette, Mills, and Lawrence (1952) showed that the alkaline phosphatase and glycogen content of leucocytes was high in polycythaemia vera and low in leukaemia.

There is now ample evidence that ionizing radiation has a leukaemogenic action (Court-Brown, 1958). In their recent work Court-Brown and Doll (1957) showed that the incidence of leukaemia in patients with ankylosing spondylitis was significantly increased after irradiation. It has also been shown that the incidence of leukaemia is increased among the atomic bomb survivors in Japan (Folley, Borges, and Yamawaki, 1952; Lange, Moloney, and Yamawaki, 1954). In recent years there has been much discussion of the possibility of an increased incidence of leukaemia following the introduction of ^{32}P therapy. Opinions are divided. Lawrence (1949) and Wasserman (1954) felt that ^{32}P therapy does not materially increase the incidence of leukaemia; and in fact, as Wasserman pointed out, since leukaemia is a stage in the natural course of the disease, all patients with polycythaemia are liable to develop leukaemia if they survive long enough. On the other hand, the majority of patients reported have at some stage of the disease been treated with some form of irradiation.

Lawrence (1955) reported 16 patients with leukaemia out of a total of 231, Hall (1948) reported four out of 124, and Wasserman (1954) found seven cases among 64 patients. The leukaemia is almost invariably myeloid, either chronic or acute. It has been thought by some workers that the use of ^{32}P therapy increases the relative incidence of the acute form of leukaemia (Wiseman, Rohn, Bouroncle, and Myers, 1951). In the present series two patients have so far developed leukaemia. It may be significant that both patients had been treated previously by external radiation.

J. L. A man aged 58 when first seen in October 1952. A diagnosis of polycythaemia vera was first made in 1942. He was given X-ray therapy at another hospital, and was later treated by venesection, the last occasion being in December 1951. On admission to Hammersmith Hospital he complained of dizziness and nervousness, abdominal discomfort, and splenic pain. He was plethoric and slightly blue; the spleen was enlarged to 5 cm. and the liver to 4 cm. below the costal margin. The peripheral blood count was as follows: red cells 8,600,000 per cu. mm.; haemoglobin 17·3 g. per 100 ml.; leucocytes 14,000 per cu. mm. (metamyelocytes 4 per cent., eosinophils 3 per cent., neutrophils 84 per cent., lymphocytes 9 per cent.); platelets 260,000 per cu. mm. The sternal marrow findings were consistent with a diagnosis of polycythaemia vera. There was no increase in primitive cells. He was given 7 mc of ^{32}P on 8.10.52. There was no clinical or haematological response, and a further 8 mc of ^{32}P was given on 24.3.53. A symptomatic and haematological remission occurred after the second dose, and the patient remained well until May 1954. His condition then began to deteriorate. He lost 10 kg. of weight in the next six months. The liver and spleen enlarged considerably. He was readmitted in December 1954. Examination of the marrow showed changes suggestive of acute leukaemia; two weeks later blast cells (9 per cent.) appeared in the peripheral blood. The leucocyte count was 14,000 per cu. mm., haemoglobin 11 g. per 100 ml., packed-cell volume 39 per cent., and platelets 55,000 per cu. mm. He was given splenic irradiation, which was stopped after a dose of 150 r. had been given, because petechial haemorrhages had developed and the platelet count had fallen to 20,000 per cu. mm. His condition deteriorated rapidly, and he died on 2.2.55. Permission for autopsy was refused.

P. P. A man aged 49 when first seen in October 1950. The diagnosis of polycythaemia vera was first made in 1941 while the patient was in the Army. He was given X-ray therapy to the long bones at that time, and again in 1948 and 1949 at another hospital. When first seen his main complaints were left-sided abdominal pain, dizziness, lassitude, and paraesthesiae in the fingers and toes. He was markedly plethoric; the liver was not felt, but the spleen was just palpable below the costal margin. A blood count showed: red cells 7,300,000 per cu. mm.; haemoglobin 21·6 g. per 100 ml.; packed-cell volume 66 per cent.; leucocytes 14,000 per cu. mm., with 81 per cent. neutrophils (no primitive cells seen); platelets 130,000 per cu. mm. The appearance of the marrow was characteristic of polycythaemia vera. In November 1950 he was given 7 mc of ^{32}P, and further doses were given at intervals over the next four years; a total of 57 mc was given. Although he was relatively well for short periods, he was never considered to have had a complete remission. In May 1955 the blood picture suggested that chronic myeloid leukaemia was developing; this was confirmed by marrow puncture two months later. During the following five months he felt

remarkably well; this subjective improvement was no doubt due to the reduction in the red-cell mass as a result of the leukaemic process.

In October 1955 his general condition deteriorated, and the haemoglobin level fell to 9 g. per 100 ml. The leucocyte count was 144,000 per cu. mm., with 28 per cent. primitive cells. He was admitted to hospital, and was treated with busulphan over a period of six weeks. The leucocyte count fell to 11,000 per cu. mm., with 2 per cent. primitive cells, and he felt considerably better. In January 1956 he developed pain in the lower back and both hip regions. X-rays showed osteolytic lesions in the left ileum and the right lesser trochanter. He was given a short course of X-ray treatment to the deposits, with relief of pain. In February 1956 he developed haematuria, and on 10.3.56 he was admitted with anuria due to uric acid calculi in both ureters. A laparotomy was performed; the patient died during the operation. Autopsy confirmed the diagnosis of leukaemia and uric acid calculi.

The incidence of leukaemia in patients treated with ^{32}P will become apparent with the longer period of follow-up in the next decade, but the only real basis for comparison would be with a control series of patients treated by some method other than irradiation and equally effective. It is evident that, if there is a natural association between polycythaemia and leukaemia, the incidence of the latter will be increased as the life span of the patients is prolonged.

Myelosclerosis

The relationship between myelosclerosis and polycythaemia is similar to that which exists between leukaemia and polycythaemia. It is known that polycythaemia may terminate in the anaemia of myelosclerosis, with extramedullary haemopoiesis (Wasserman, 1954; Steinfield and Beizer, 1954). During the last two years two patients referred with a diagnosis of polycythaemia were shown on further investigation to have myelosclerosis. A further two patients who had clear evidence of polycythaemia in the past, but did not receive any treatment, were seen during the late stages of myelosclerosis. Only one of the 90 patients treated with ^{32}P has so far developed myelosclerosis.

Discussion

Polycythaemia vera is generally considered to be a rare disease. It is undoubtedly uncommon, but this fact has perhaps been overstressed in medical teaching, and as a result the diagnosis is frequently missed. Although ^{32}P was first used in 1938, it was not available in Europe until the late 1940's, and even today there are large areas of the world in which isotope therapy is still not available. Yet by 1953, at the International Congress of Radiology, 2,140 cases treated with ^{32}P were reviewed (Low-Beer, 1954). Polycythaemia vera usually runs a chronic course. There are well authenticated reports of patients having lived up to 20 years without treatment. On the other hand, while every large series includes many patients with long survival, Tinney, Hall, and Giffin (1945) reported that in a group of patients from the Mayo Clinic less than 25 per cent. lived longer than five years from the time when the diagnosis was first

established; Videbaek (1950) analysed the data from 125 patients treated by miscellaneous methods, but not by radioactive phosphorus. A calculation based on his figures shows a median survival of 6·6 years. The prognosis appears different for men and women in his series, namely a median survival of 4·4 years for men and 8·6 years for women. As mentioned above, haemorrhage and thrombosis are the most common causes of death; treatment which will reduce the red-cell mass and control the number of platelets undoubtedly prolongs life. It is most important to stress that the diagnosis of polycythaemia vera must be clearly established before starting treatment. Secondary polycythaemia is usually a compensatory response to conditions of anoxia, and treatment of this type of polycythaemia with ^{32}P may be harmful to the patient. Secondary polycythaemia is more common than polycythaemia vera. In some patients with polycythaemia vera the erythraemia is not accompanied by leucocytosis or thrombocytosis. In the present series 16 patients out of 90 (18 per cent.) had both leucocyte and platelet counts which were within normal limits (Fig. 5). In such cases diagnosis is often difficult, and is arrived at through excluding secondary polycythaemia by such tests as that of oxygen saturation in arterial blood, as well as by the diagnostic features of bone biopsy, blood-volume estimations, and other relevant investigations. As a rule the elevation of the red-cell count is less marked in secondary polycythaemia.

Until the aetiology of polycythaemia vera is clarified and treatment can be directed to the fundamental cause, radioactive phosphorus provides a very satisfactory method of control. Eighty-two per cent. of our patients obtained full remission, and this figure could probably be increased if a more vigorous treatment policy were pursued. There was a small group of patients (probably about 5 per cent.) who were unusually refractory to this form of therapy. Similar resistance to ^{32}P has been noted by other workers (Wiseman, Rohn, Bouroncle, and Myers, 1951; Harman, Hart, and Ledlie, 1955). In such patients repeated venesections or chemotherapy may be the only practical alternatives. The single-dose technique has certain advantages. The time of treatment is short. Sixty-nine per cent. of the patients who were considered to have a full remission obtained it after a single injection. The longer period of remission compares favourably with that obtained by other techniques. Constitutional effects due to radiation sickness do not occur. Although full haematological remission is not usually achieved in less than two to four months after injection, symptomatic improvement usually occurs much earlier. Of special interest has been the group of patients in whom thrombocythaemia dominated the clinical picture. Three of these patients obtained only a partial remission, and in the other five, though full remissions were achieved, they were of shorter duration than the average. We consider that this group is less sensitive to treatment.

It is not yet possible to estimate the degree of prolongation of life in our series, as the majority of the patients have not been observed for a sufficiently long period. Lawrence (1955) analysed the results in 231 patients (73 of whom had died) treated since 1938, and obtained a median survival of 13·3 years. He concluded that the expectation of life of patients with polycythaemia vera was

only a few years less than the normal for a population of a similar age group, and optimistically pointed out that the prognosis was comparable to that of patients with diabetes mellitus or pernicious anaemia who receive specific therapy. We consider that it is too early to reach a final conclusion about the place of ^{32}P in the treatment of polycythaemia vera. A longer time interval, and the collation and analysis of further reports of the results of treatment, are needed. More information is required about the leukaemogenic action of radioactive phosphorus. It would also be advantageous if the dosimetry of the isotope could be placed on a more scientific basis. In our present state of knowledge, however, ^{32}P remains the treatment of choice for the majority of patients with polycythaemia vera.

We wish to thank Dr. Constance Wood and Professor J. V. Dacie for their advice and criticism. We are indebted to the physicians who referred patients for treatment. We are grateful to Mr. F. G. Mason, Miss J. M. Gartside, and Miss N. D. White for technical assistance. One of the authors (L. S.) has been in receipt of a grant from the British Empire Cancer Campaign during the latter part of this work.

Summary

1. The symptomatology and clinical findings in 90 patients with polycythaemia vera treated with ^{32}P are described.

2. The haematological data, including blood-volume measurements, are given; special attention is paid to patients with normal platelet and leucocyte counts, and to patients who had platelet counts persistently raised above 1,000,000 per cu. mm.

3. Methods of treatment before the introduction of ^{32}P are briefly reviewed.

4. The technique and dosage problems of ^{32}P therapy are discussed, and the results obtained in the first 78 patients presented.

5. The problem of leukaemia and myelosclerosis in relation to polycythaemia vera and to ^{32}P is discussed.

6. It is concluded that at the present time ^{32}P is the treatment of choice in polycythaemia vera.

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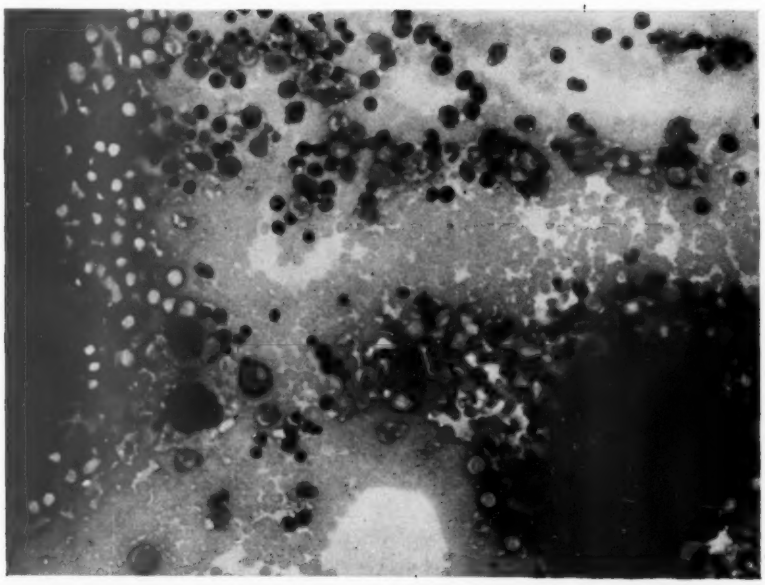

FIG. 11. Bone marrow smear showing increased cellularity, with loss of fat spaces, in the fragments (×100)

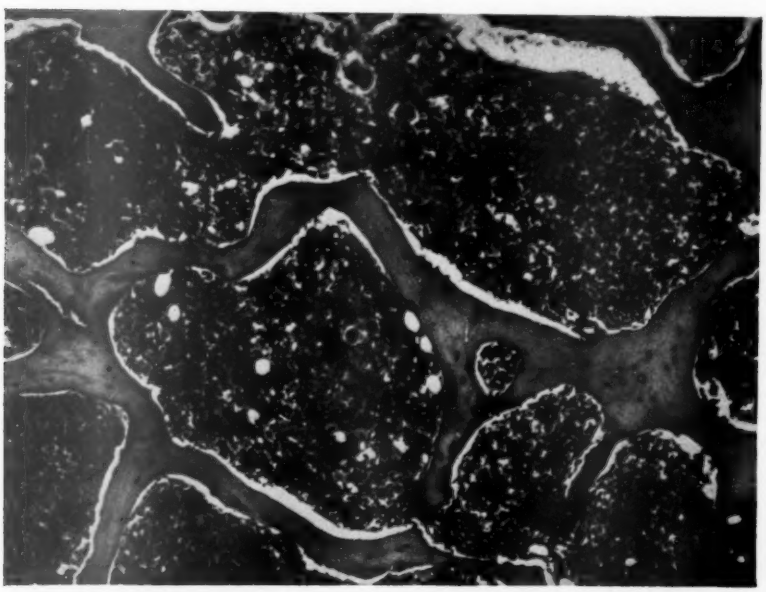

FIG. 12. Bone biopsy section showing loss of fat spaces and increased cellularity (×100)

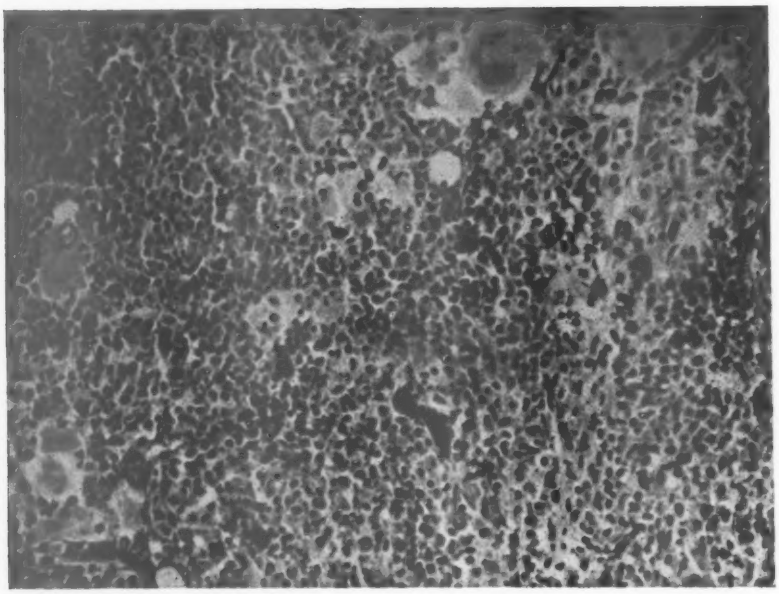

FIG. 13. Bone biopsy section from a patient with early myelosclerosis. Areas of fibrous tissue can be seen. Note the large numbers of megakaryocytes (× 100)

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SALT-WASTING RENAL DISEASE[1]

Metabolic Observations on a Patient with 'Salt-losing Nephritis'

By S. W. STANBURY and R. F. MAHLER

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In the 14 years since the syndrome was defined by Thorn, Koepf, and Clinton (1944), some dozen or more patients with 'salt-losing nephritis' have been described in clinical detail. Fragmentary metabolic studies have been made of some of these patients (Murphy, Coffman, Pringle, and Iseri, 1952; Cleempoel and Karkhausen, 1957; Knowles, Levitin, and Bridges, 1957), but usually their precarious clinical state has prevented planned and detailed investigation. The present report describes a comprehensive metabolic study of a single patient. We interpret the results to indicate that 'salt-losing nephritis' is simply an unusual variant of chronic azotaemic renal failure. The excessive renal loss of sodium and chloride can be explained satisfactorily without the need to invoke the occurrence of a specific disorder of renal tubular function.

Case Report

The patient was an unmarried woman, 32 years old in 1954, who gave no history of past renal disease or of renal symptoms. During the previous year she had experienced intermittent lumbar pruritus and muscular cramps in the feet. For several years she had been accustomed to drink copious amounts of fluid and admitted to taking up to 15 breakfast-cups (about 7 oz., or 200 ml., in capacity) of tea in the course of a day; this she dismissed as personal idiosyncrasy. In February 1954 two wisdom teeth were extracted under local anaesthesia. The surgery was uncomplicated, but she vomited frequently during the following day, and thereafter she developed progressive lassitude. On getting up after a few days' rest in bed she experienced severe postural giddiness, and was unable to keep her balance with the eyes closed. These symptoms, and a troublesome nausea, improved sufficiently within a month to permit her to return to part-time work, but she remained in poor health, and lost about 10 lb. in weight. She was easily tired and dyspnoeic on exertion; a rapid change of posture would produce giddiness and sometimes a transient impairment of vision. Vomiting commenced again on 27.5.54, and she was admitted to Macclesfield Hospital under the care of Dr. F. Wemyss Smith.

Examination revealed a slim, although well-nourished, woman with a moderate degree of anaemia. The facial skin was faintly bronzed, and the nipples and areolae were dark, but there was no abnormal pigmentation elsewhere. The arterial blood-pressure was 120/80, falling to 90/50 on standing. Otherwise

[1] Received August 25, 1958.

the physical findings were normal, and the urine contained no protein. The serum sodium was diminished (135 m-equiv. per litre) and the serum potassium increased (9·1 m-equiv. per litre); the blood-urea level was 115 mg. per 100 ml., the haemoglobin 9 g. per 100 ml., and the erythrocytes 3,230,000 per cu. mm. The electrocardiogram showed the peaked T waves of hyperkalaemia. In the absence of renal symptoms and proteinuria, a diagnosis of Addison's disease was made and appropriate therapy instituted. The patient's clinical condition improved rapidly after transfusion of blood and saline solutions; and specific treatment was started with the daily intramuscular injection of 25 mg. of cortisone and 10 mg. of deoxycortone, together with 8 g. of sodium chloride daily by mouth. Within a week the serum level of potassium had reached values of 3·6 to 5·1 m-equiv. per litre, and the electrocardiogram became normal. The blood-pressure was maintained at about 120/70, and there was no longer a postural hypotension.

It was then noted that, although there was no complaint of nocturia, the patient was passing about one litre of urine during the night. The daily volume of urine, which was about 1·5 litre on her first admission to hospital, had increased to three litres, yet the blood urea remained at 100 mg. per 100 ml. It was realized that the patient might have a salt-wasting renal lesion, and careful testing of the urine revealed an occasional trace of protein, but no formed elements. Steroid therapy was stopped, and the patient was maintained on 10 g. sodium chloride daily by mouth. She appeared to be less well when not receiving cortisone, and it was felt that the possibility of combined renal and adrenal insufficiency had not been excluded. Consequently, on leaving hospital, she was given a daily oral dose of 25 mg. of cortisone in addition to her supplement of salt. Two weeks later, in the out-patient clinic, she was complaining of slight oedema of the ankles at the end of the day, and blood examination showed the serum sodium to be 152 m-equiv. per litre and serum chloride 113 m-equiv. per litre. Subsequently the daily supplement of salt was reduced to 8 g. and then, on 29.7.54, to 5 g.; the administration of cortisone was also stopped. At the beginning of September she again developed nausea, hiccough after eating, profound tiredness, and cramps in the feet. The serum sodium was 130 m-equiv. per litre, and the serum chloride 102 m-equiv. per litre. It was decided to admit her to the Manchester Royal Infirmary for metabolic investigation, and in the meantime her daily salt supplement was increased to 8 g.

The metabolic investigations were carried out during October and November 1954. After her subsequent discharge she remained in good health when receiving 12 g. NaCl and 8 g. $NaHCO_3$ daily, together with the liberal use of table salt. She was readmitted to hospital for further metabolic study in December 1955. Clinical deterioration, with increasing blood-pressure and azotaemia, began in the summer of 1956, and she died at home of uraemia in the autumn of that year. No autopsy was obtained.

Metabolic Investigation

Methods

The patient's chosen diet was found by analysis to contain: N, 13·3 g.; Na, 1·57 g. (68·5 m-equiv.); Cl, 2·57 g. (72·5 m-equiv.); K, 2·34 g. (60 m-equiv.). No table salt was added to meals, and the patient's customary 8 g. supplement of sodium chloride was withdrawn on the second day in hospital ('day 1' of the metabolic study). Dietary rejects were analysed chemically. Daily urinary

specimens and all stools were analysed for N, Na, K, and Cl, but no attempt was made to determine external balances of calcium and phosphorus, since faeces were passed irregularly in the form of small hard pellets. The metabolic, isotopic, and chemical methods used were as described elsewhere (Mahler and Stanbury, 1956; Stanbury and Macaulay, 1957). Experimental results are presented in diagrammatic and tabular form, and comment is limited to necessary amplification of these data. For convenience of reference, and to avoid reiteration in subsequent description, the imposed changes of sodium intake are summarized in Table I.

TABLE I

The Changes of Sodium Intake

Day	*Change of therapeutic regimen*	*Total daily Na intake (m-equiv.)*
1	Withdrawal of 8 g. NaCl supplement	
1–4	Dietary intake only	68
5–11	Diet+8 g. NaCl	204
12–17*	Diet+8 g. NaCl+7·5 g. $NaHCO_3$	*about 290
17	Intravenous infusion NaCl+Na lactate†	975
18 on	Light diet +12 g. NaCl+7·5 g. $NaHCO_3$	324

* During the last days of this period much food was rejected; this was analysed, and the actual intake accurately determined.

† 345 m-equiv. of NaCl+230 m-equiv. of sodium lactate in 3 litres of water.

Clinical effects of sodium deprivation. No adverse effects were apparent until the morning of the fifth day. The patient had vomited once during the previous night, and the blood-pressure fell from its original value of 130/80 to a systolic level of 105; the daily output of urine had dropped to two litres (Fig. 6). The eyes were a little sunken, but there were no other physical changes accompanying the loss of 380 m-equiv. of sodium (Fig. 2). She had, however, developed symptoms typical of severe sodium depletion, as described by McCance (1936). Most conspicuous were her profound inertia and her conversion from an alert, happy and intelligent woman into an apathetic creature who slept frequently. She was anorexic and nauseated, and had to reject some food; but her principal complaint was of the condition of her mouth. She was not thirsty, but her mouth felt dry, and the mucosal surfaces and saliva were sticky. The lips were dry, and began to crack. Neither the addition of a daily supplement of 8 g. of NaCl (day 5) nor the later provision of a further 7·5 g. of $NaHCO_3$ daily (day 12) produced satisfactory clinical improvement. The condition of the mouth was causing her considerable distress, and on the 15th day necessitated a fluid diet. On the same day she vomited once, and the serum urea reached its highest level of 324 mg./per 100 ml. (Fig. 1). It was proved subsequently that the original deficit of sodium had been made good by the 15th day (see Fig. 2), but it was then our clinical impression that the administration of additional sodium by parenteral injection was imperative. Consequently she was given a large infusion of isotonic sodium chloride with added molar sodium lactate (Table I). For a short time after the infusion she experienced a sensation of 'electricity all over', but no clinical signs of tetany were detected. On the

following day the blood-pressure was 160/80, but this elevation was temporary, and it subsequently remained at about 120/70. Within 48 hours of her infusion the patient felt well and was normally active.

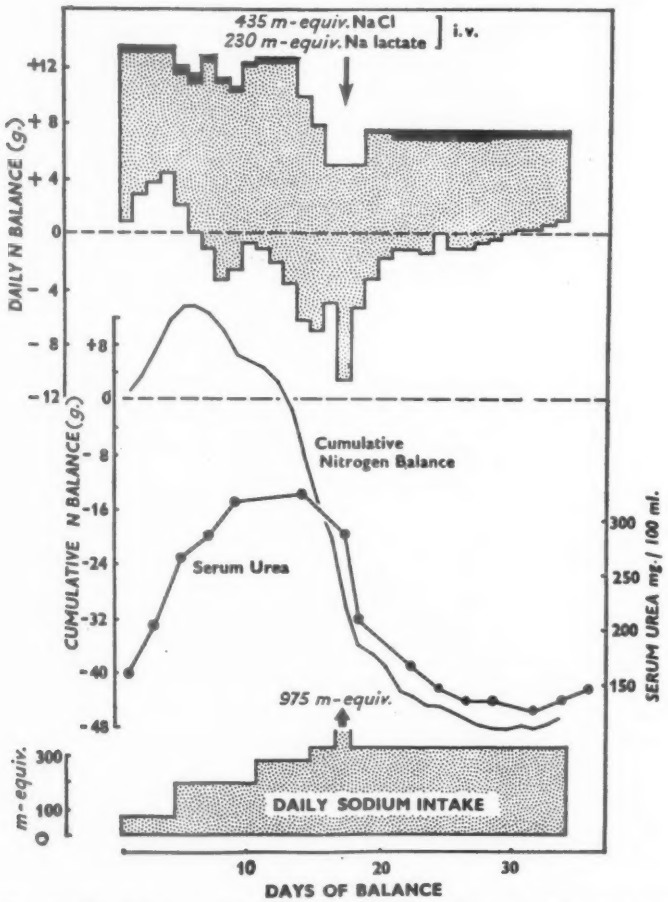


FIG. 1. The daily external balance of nitrogen, and the relationship between the serum level of urea and the cumulative nitrogen balance.

(In this diagram and Fig. 5 the dietary intake is indicated by the height of the columns above the interrupted base-line; faecal (black) and urinary (stippled) output are charted sequentially downwards from the intake line. A positive balance is represented by an enclosed white area above, a negative balance by a stippled area below, the base line).

Nitrogen metabolism (Table II; Fig. 1). Withdrawal of the 8 g. supplement of sodium chloride was followed by a progressive rise in the serum-urea level, which was due partly to the renal retention of urea and partly to breakdown of tissue protein. The nitrogen retained during the first five days was sufficient to account for the increased serum urea; subsequently, with the increased

intake of sodium, the urinary output of nitrogen increased, and from the seventh day onwards the daily external balance of nitrogen was negative (Fig. 1).

The serum urea continued to increase, and reached 324 mg. per 100 ml. on the 14th day, by which time the *cumulative* external balance of nitrogen had also become negative (Fig. 1). It is estimated that the total catabolic production of urea nitrogen between the fourth and 14th days was approximately 46 g. (Table II), equivalent to the loss of about 0·29 kg. of body protein. No further catabolic production of urea was apparent after the cumulative balance of

TABLE II

Changes in Serum Urea, Urea Clearance, and External Nitrogen Balance

Day	Serum urea (mg./100 ml.)	Urea clearance (ml./min.)	ΔN (g.)	Δurea derived from tissue breakdown (g. (≡ g. N))		ΔNa (m-equiv.)	Serum total CO_2 (m-moles/l.)
1	154	11·5	+0·77	Nil	..	−165	20·4
3	204	6·7	+7·1	Nil	..	−333	18·2
5	262	5·3	+13·4	4·3	(2·0)	−320	..
7	271	7·5	+12·3	9·5	(4·4)	−268	17·1
9	318	5·9	+6·4	66	(31)	−254	15·3
14	324	7·4	−7·9	99	(46)	−79	17·3

ΔN and ΔNa represent the cumulative changes in external balance of nitrogen and sodium. Urea clearance was calculated from the 24-hour urinary output of urea and the corresponding plasma level (UV/P).

Δurea is a derived value, calculated from the change of external nitrogen balance and the simultaneous change in plasma-urea level. It is assumed that body urea was distributed in the total body water, which is taken as equivalent to 50 per cent. of body weight (Edelman, Haley, Schloerb, Sheldon, Friis-Hansen, Stoll, and Moore, 1952). The tabulated figures represent the cumulative contribution that was made to the increase of total body urea by endogenous protein catabolism.

Data for sodium balance and serum-bicarbonate level are included for comparison with the other changes.

sodium became positive on the 15th day, and the subsequent progressive fall in the serum-urea level was accounted for fully by the negative external balance of nitrogen (Fig. 1). When nitrogen equilibrium was finally achieved, the serum-urea level was 135 mg. per 100 ml., and the total cumulative loss of nitrogen was 48 g. (Fig. 1). Although observations were continued for a further 10 days, there was no evidence that nitrogen was being retained to rebuild the lost protein. The haemoglobin level, which was 9·2 g. per 100 ml. before the period of salt deprivation, fell to 6·8 g. as the azotaemia increased. No evidence of blood regeneration was seen during the 14 days following restoration of body sodium, and it was necessary to give the patient a transfusion before she left hospital.

Potassium and phosphorus metabolism (Figs. 2, 3, 4, and 5). When observations were commenced the serum potassium was 5·4 m-equiv. per litre, and the total exchangeable body potassium (K^e) was 2,550 m-equiv., or 41·6 m-equiv. per kg. of body weight. The daily external balance of potassium was negative (Fig. 5), and the measured loss in 17 days was 240 m-equiv. During this time the K^e had fallen by 300 m-equiv. to 2,250 m-equiv. (37·4 m-equiv. per kg.).

After the saline infusion on the 17th day the patient remained in potassium equilibrium. Assuming that 3 m-equiv. of potassium is equivalent to 1 g. of tissue-protein nitrogen, about 140 m-equiv. of the negative potassium balance

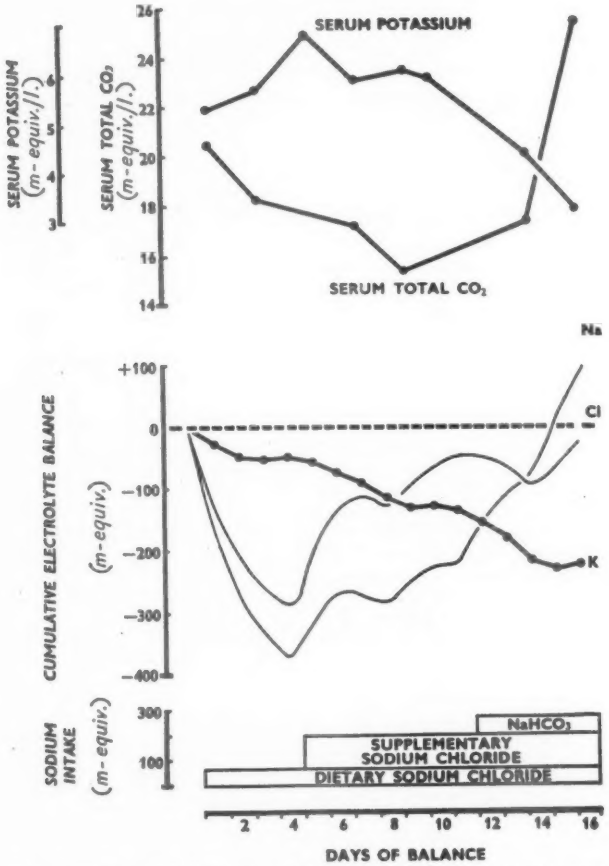
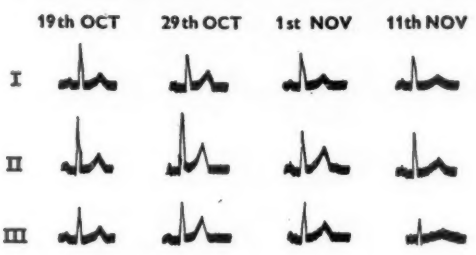


FIG. 2. The cumulative external balances of sodium, chloride, and potassium. Note (1) that changes in the serum level of potassium were largely independent of the external balance of potassium, and (2) the generally inverse relationship between the serum levels of total CO_2 and potassium.

can be accounted for on the basis of tissue breakdown; the fall in the serum level of potassium would account for a further 25 m-equiv. The remainder of the negative balance probably represented potassium released from cells as a result of the developing metabolic acidosis. It was evident that variation in the serum level of potassium was largely independent of the external balance of potassium (Figs. 2 and 3). There was a significant inverse correlation between the serum levels of total CO_2 and those of potassium (Fig. 4A), suggesting that

the latter were determined principally by shifts of potassium between cells and extracellular fluid with changes of acid-base balance. Such a relationship would be in agreement with experimental evidence of various kinds (Stanbury and



Serum K^+ (*m-equiv./l.*)	5·4	6·1	4·5	3·1
Serum CO_2 (*m-equiv./l.*)	20·4	14·1	17·3	31·4
Cumulative K Balance (*m-equiv.*)	Start	-142	-225	-241
Cumulative Na Balance (*m-equiv.*)	Start	-231	-79	+>700

FIG. 3. The relationship between electrocardiographic changes, serum-electrolyte levels, and the external balances of sodium and potassium.

(In the column dated 11th November the figure for the external balance of sodium is approximate; the dietary intake of sodium could not be measured precisely at this time.)

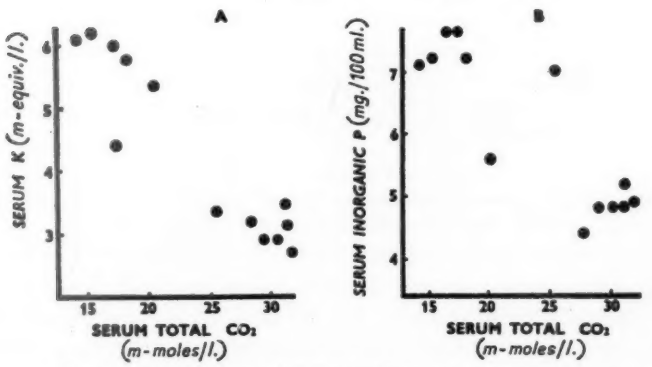


FIG. 4. The inverse relationship between the serum levels of total CO_2 and of potassium (A) and inorganic phosphate (B).

Thomson, 1952; Scribner, Fremont-Smith, and Burnell, 1955; Darrow, 1957), and is perhaps to be expected in a patient apparently incapable of varying significantly the urinary output of potassium (see p. 437).

The measured urinary output of phosphorus varied slightly with changes of

the urea clearance, but the serum phosphate varied markedly, and roughly in parallel with the serum potassium (Fig. 5). The serum phosphate was also inversely related to the serum total CO_2 (Fig. 4B), suggesting that it was subject to the same extrarenal influences as potassium.

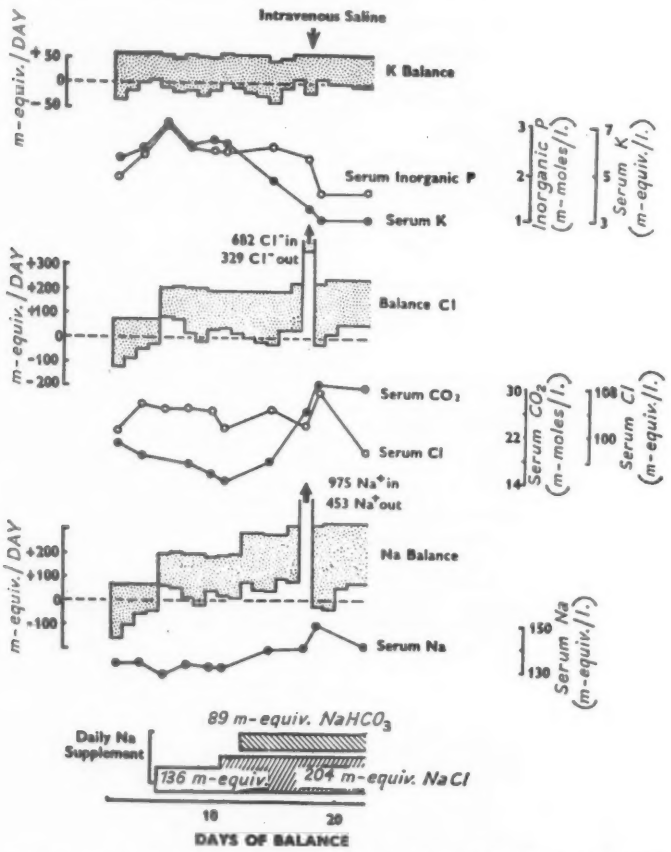


FIG. 5. The daily external balances of potassium, chloride, and sodium, with the corresponding changes in serum levels.

(Note that the scale for potassium is twice that for sodium and chloride).

Sodium and chloride metabolism (Figs. 2 and 5). Although large amounts of sodium and chloride (380 m-equiv. Na, 292 m-equiv. Cl; see Fig. 2) were lost during the four days of restricted salt intake, cumulative wastage was limited by a progressive reduction in their urinary output. The rate of excretion of each ion was almost exactly halved between the first and fourth days, and the daily negative balance was correspondingly greatly reduced (Fig. 5). By the fifth day the serum level of sodium had fallen to 128·5 m-equiv. from 133·5 m-equiv. per litre; the serum chloride remained at 100 m-equiv. per litre. Sodium and chloride were retained when their intake was again increased (see

Table I), and the cumulative external balance of sodium was positive by 82 m-equiv. on the 16th day (Fig. 2). In spite of this, a further 522 m-equiv. of sodium and 333 m-equiv. of chloride were retained during the 24 hours following the saline infusion on the 17th day. Making the assumption that chloride did not penetrate into cells, it was calculated that the volume of the extracellular fluid was expanded by three litres, of which one litre was derived from the intracellular fluid. No significant amount of the retained sodium appeared to enter cells and, in spite of the expanded volume of the extracellular fluid, there was no apparent tendency to excrete the retained sodium chloride (Fig. 5). This suggests that the patient may already have been significantly deficient of sodium when metabolic studies were commenced, and the low serum-sodium level (133 m-equiv. per litre) at that time would be compatible with this explanation. A previously existing deficiency would also account for the severity of clinical symptoms resulting from a measured loss of sodium of less than 400 m-equiv.; in McCance's (1936) experimental study of salt deficiency a deficit close to 800 m-equiv. produced symptoms of comparable severity.

After the saline infusion the patient was maintained on a daily supplement of 12 g. NaCl and 8 g. $NaHCO_3$, and with this therapeutic regimen the serum-electrolyte levels remained within normal limits.

Adrenal function and its relation to electrolyte balance. The urinary output of 17-ketosteroids (4·2 mg. to 10·6 mg. per 24 hours) and 17-ketogenic steroids (8 mg. per 24 hours) was normal. Corticotrophin, in a single intramuscular dose of 50 mg., reduced the circulating eosinophils from 340 to 80 per cu. mm. in four hours. At the end of the metabolic studies described above the patient was given deoxycortone by intramuscular injection, a total dose of 70 mg. in four days. During this treatment the mean daily output of sodium in the urine was 242 m-equiv., as compared with a mean of 265 m-equiv. during the three days after withdrawal of the steroid. On each of the following three days she received 100 mg. of corticotrophin intramuscularly, and the mean daily output of sodium was 255 m-equiv. These results suggest a minor response to adrenal steroids, but the differences observed are barely outside the cumulative errors of collection and analysis. The urinary output of potassium was uninfluenced by either deoxycortone or corticotrophin.

In December 1955 further metabolic observations were made during a six-day period, on the first day of which the urinary output of aldosterone and cortisol were determined by Dr. A. H. Gowenlock, using the physicochemical method of Ayres, Garrod, Simpson, and Tait (1957). The output of aldosterone was 10 times the average found in normal subjects (Table III). At the time of hormonal assay it was considered that the patient was not deficient of sodium. For a year she had been receiving a daily supplement of 12 g. NaCl and 8 g. $NaHCO_3$; and throughout this time she had been judged on clinical grounds to be replete with sodium. On the day of hormonal assay the serum level of sodium was 141 m-equiv. per litre, of potassium 5·7 m-equiv. per litre, and of urea 213 mg. per 100 ml.; the blood-pressure was 165/95 mm.; the total exchangeable body sodium (Na^e), measured by isotopic dilution with ^{22}Na, was 2,320

m-equiv., or 36·7 m-equiv. per kg. of body weight. This value of Na^e, and the mean value of 2,300 m-equiv. obtained during the following six days, are well within the normal range (Edelman, James, Brooks, and Moore, 1954). During the balance study, with a daily sodium intake of 335 m-equiv., the average daily output of sodium in the urine was 350 m-equiv.; this is regarded as indicating effective external balance for sodium. The dietary intake of potassium was 47 m-equiv., and the average daily urinary output of potassium was 57 m-equiv.; as was revealed in the previous metabolic study, there appeared to be a failure

TABLE III

The Urinary Output of Aldosterone and of Cortisol (Hydrocortisone)

	December 1955	*March 1956*
Urinary volume	3,580 ml.	3,540 ml.
Daily output of sodium	350 m-equiv.	425 m-equiv.
Daily output of potassium	57 m-equiv.	58 m-equiv.
24-hour urinary aldosterone	107 μg.	134 μg.
24-hour urinary cortisol	25 μg.	43 μg.
24-hour urinary corticosterone	..	3 μg.

The first assay was performed by Dr. A. H. Gowenlock, the second by Drs. J. F. Tait and S. A. Simpson.

Normal values for the urinary output of the three steroids are given by Ayres, Garrod, Simpson, and Tait (1957) as follows:

	Aldosterone	*Cortisol*	*Corticosterone*
Mean and range (μg./24 hours)	11 (4·6–23·5) (31 subjects)	35 (13–86) (24 subjects)	5·8 (2·2–9·0) (7 subjects)

It will be noted that in the patient only the output of aldosterone was greatly increased; the output of cortisol and corticosterone remained well within normal limits. (Dr. Gowenlock (personal communication) has assayed the output of adrenal steroids in another patient with chronic azotaemia and the 'salt-wasting syndrome'. At the time of assay the patient was receiving an apparently adequate supplement of sodium, but no metabolic studies were made. The urinary output of aldosterone was 143 μg. per 24 hours with a daily sodium intake of 250 m-equiv.).

to conserve potassium in the face of a relatively low intake. There was thus little ground for believing that either a contemporary deficiency of sodium or an abnormal retention of potassium was responsible for the greatly increased urinary output of aldosterone. Hormonal assay was repeated in March 1956, when the patient was again at home and fully active. She was then excreting even greater daily amounts of sodium as a consequence of increased dietary intake, but the results of hormonal assay were essentially the same (Table III).

Observations on Renal Function

No formed elements were found on microscopic examination of the urine, proteinuria was minimal or absent, and there was no glycosuria. X-ray tomography of the renal areas revealed a normal kidney outline, with no radiologically demonstrable cysts; the apparent renal dimensions were 10×5 cm. and 8×5 cm. Certain aspects of the functional performance of the diseased kidneys are depicted in Figs. 6, 7, and 8, and Table IV.

Plasma and urinary osmolarity: isosthenuria. During the period of salt

deficiency the rise in osmolar concentration of urea in the plasma was greater than the fall in osmolar concentration of sodium. Consequently the osmolarity

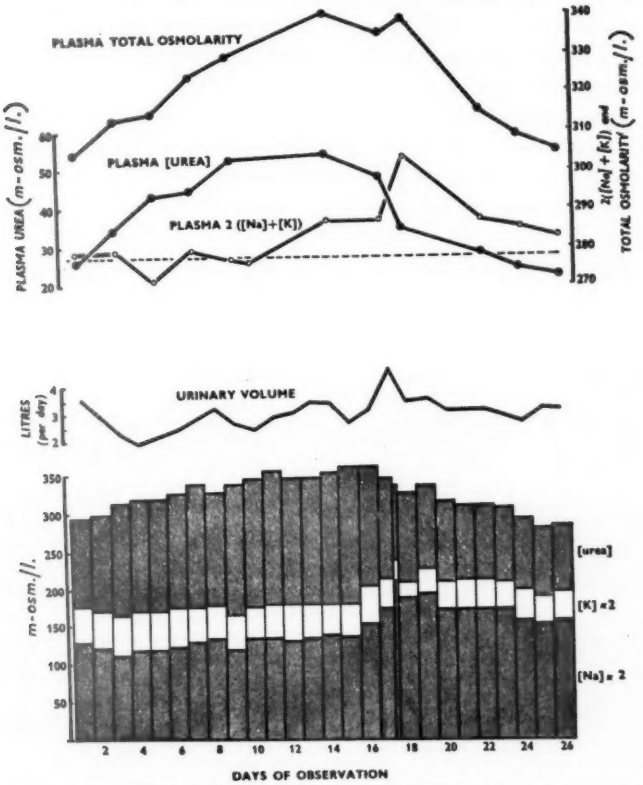


FIG. 6. The relationship between the osmolarity of the plasma and the osmolarity of the urine after withdrawal of supplementary sodium chloride, and during the replacement of sodium.

Osmolarity is here calculated as 2 ([Na]+[K])+[urea].

The urinary data refer to 24-hour collections, and the total osmolarity is represented by the height of each column. The osmotic contributions of sodium, potassium and urea are indicated separately. At this rate of urinary flow it is considered that the calculated figure for osmolarity approximates very closely to the true value. The interrupted line in the upper part of the diagram indicates the plasma level of urea and electrolytes at the start of observation.

(Urea made the greatest contribution to urinary total osmolarity during the first 14 days, suggesting that it was then the principal solute maintaining osmotic diureses. After the saline infusion (day 17) sodium became the principal urinary solute, as would be expected during an osmotic diuresis with sodium as the 'loading solute'.)

of the body fluids increased, and there was a corresponding increase both in the total osmolarity of the urine and in the urinary concentration of urea (Fig. 6). These changes were reversed with sodium replenishment, when the urinary concentration of sodium increased at the expense of the concentration of urea.

Throughout the period of observation the osmolarity of the plasma, calculated as 2([Na]+[K])+[urea], varied from 303 to 340 m-osmoles per litre, and the calculated osmolarity of the corresponding 24-hour urinary specimens varied between 280 and 360 m-osmoles per litre. The plasma and urinary values varied together in a linear manner (Fig. 6), and the higher values were obtained immediately after the hypertonic saline infusion. At all plasma levels there was a roughly linear relationship between the plasma and urinary concentrations of individual solutes, none of which was concentrated much more than four times in its passage from plasma to urine (Fig. 7).

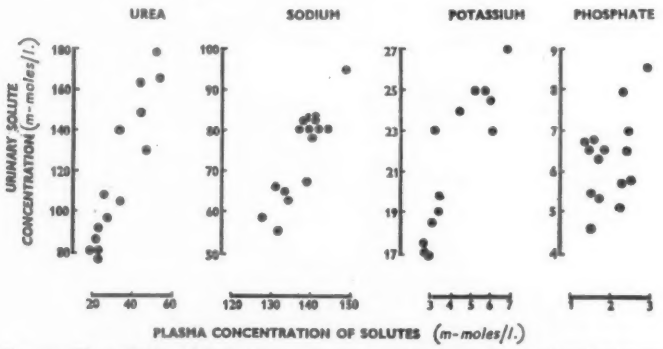


FIG. 7. The relationship between the concentration of individual solutes in the plasma and their concentration in corresponding 24-hour-samples of urine.

The changes in urinary concentration of sodium with changes of plasma sodium are small but none the less definite.

The renal handling of sodium. The plasma-to-urine concentration ratio of sodium (sodium P/U) varied only from 2·2 to 1·7, in spite of changes in external sodium balance ranging from −380 to +600 m-equiv. and a variation in the serum-sodium level from 128 to 149 m-equiv. per litre. When the patient was replete with sodium, 15 per cent. of the sodium filtered by the glomeruli was excreted in the urine (Table IV).

Urinary volume: osmotic saline diuresis. The daily volume of urine varied between 1·96 and 4·74 litres (Fig. 6) and, because of the isosthenuria, the urinary flow was determined by the load of osmotically active solute excreted. The increase in urinary volume and the fall in blood-urea level which followed correction of the deficiency of sodium resulted in part from expansion of the extracellular fluid and increase in the rate of glomerular filtration (Table IV). Another factor of probably equal significance in producing these effects was the increase in the serum level of sodium; the difference between the levels found in salt deficiency and after the hypertonic saline infusion was as great as 20 m-equiv. per litre. (In experiments on the dog, Wesson (1952) claimed that increase in the plasma concentration of sodium is more effective in promoting sodium excretion than a comparable increment in the filtered load of sodium produced by increase of the glomerular filtration rate only.) The combined

effect of the two factors was to increase greatly the filtered load of sodium entering the nephron; the unabsorbed sodium, acting as an osmotic diuretic, diminished the tubular reabsorption of water and urea (Fig. 6). The net effect on the urine resembled that occurring during an osmotic saline diuresis in individuals with normal kidneys (Rapoport, West, and Brodsky, 1949; McCance, 1945).

TABLE IV

Renal Clearance Data

A. Sodium replete, three weeks after saline infusion; receiving daily supplement of 12 g. NaCl and 8 g. $NaHCO_3$:

Renal clearance (ml./min.)		*Clearance ratio*		*Plasma level of solute*
Inulin (C_{in})	10·5	(Inulin U/P)	3·8	..
Creatinine (C_{cr})	12·7	..	..	6·1 mg./100 ml.
Urea (UV/P) (C_u)	8·2	(C_u/C_{in})	0·78	24·3 m-moles/l.
		(C_u/C_{cr})	0·65	
Sodium (C_{Na})	1·62	(C_{Na}/C_{in})	0·15	139 m-equiv./l.
		(C_{Na}/C_{cr})	0·13	
Potassium (C_K)	8·3	(C_K/C_{in})	0·79	3·5 m-equiv./l.
Chloride (C_{Cl})	1·7	(C_{Cl}/C_{in})	0·16	93·5 m-equiv./l.
Bicarbonate (C_{HCO_3})	1·2	(C_{HCO_3}/C_{in})	0·11	33·4 m-equiv./l.

B. When 380 m-equiv. deficient in sodium:

Renal clearance		*Clearance ratio*		*Plasma level of solute*
Creatinine	10·2	..	..	7·3 mg./100 ml.
Urea (UV/P)	5·3	C_u/C_{cr}	0·52	45 m-moles/l.
Sodium	0·71	C_{Na}/C_{cr}	0·07	128·5 m-equiv./l.

Note the apparent increase in the tubular reabsorption of sodium (as indicated by the lower value of C_{Na}/C_{cr}) when the patient was deficient in sodium.

Among the cases of renal failure studied by Platt (1950), those with plasma levels of creatinine between 6 and 8 mg. per 100 ml. had sodium to creatinine clearance ratios (C_{Na}/C_{cr}) of 0·05 or less. Three patients with similar plasma levels of creatinine had ratios between 0·08 and 0·1, and were considered by him to be possible 'salt-wasters'.

The renal handling of potassium. The daily excretion of potassium was usually about 60 m-equiv., and varied only between 50 and 80 m-equiv. in spite of variation in the serum-potassium level between 2·7 and 6·9 m-equiv. per litre. Consequently the renal clearance of potassium, which varied between 6 ml. and 13 ml. per minute, was determined primarily by the plasma-potassium level. It approached, but did not exceed, the rate of glomerular filtration as measured by the creatinine clearance.

The renal function of acid-base regulation. In the presence of a severe acidosis (serum total CO_2 15 m-equiv. per litre) the urine was appropriately acid (pH 5·5), but the output of ammonia was low. This finding is characteristic of advanced renal failure (Wrong and Davies, 1959). In December 1955, when receiving 8 g. $NaHCO_3$ daily, the daily output of bicarbonate in the urine was about 35 m-equiv. The effects of raising the serum-bicarbonate level by infusing 250 ml. of molar sodium lactate are shown in Fig. 8 (p. 442). There was a roughly parallel increase in the plasma and urinary concentration of bicarbonate, but the maximum rate of bicarbonate excretion observed was 0·1 m-equiv. per minute, and only 85 m-equiv. of the 250 m-equiv. load were excreted in the 44

hours after the infusion. This relatively small increase in the rate of bicarbonate excretion seems to indicate that the renal tubules were able to increase the reabsorption of bicarbonate as the plasma level was increased. Such a response resembles the behaviour of normal kidneys (Pitts, Ayer, and Schiess, 1949), and is apparently characteristic of non-specific azotaemic renal failure (Roberts, Randall, Vanamee, and Poppell, 1956).

Discussion

Renal function in the syndrome of 'renal salt-wasting' and in 'chronic renal failure'. All the recorded cases of 'salt-losing nephritis' have occurred in patients with advanced renal failure and retention of nitrogen. The hypothetical possibility, that the tubular reabsorption of sodium and chloride may become defective in a patient with a normal rate of glomerular filtration, has not yet been recognized as a manifestation of primary renal disease. It is also well known that patients with chronic renal failure not infrequently develop a deficiency of salt (Peters, Wakeman, and Lee, 1929), especially if their dietary intake of sodium chloride is restricted (Landis, Elsom, Bott, and Shiels, 1935); and, because of this general tendency, it has been suggested that 'salt-losing nephritis' should not be distinguished as a separate entity. We concur with this suggestion, but consider it convenient to retain the term to define both a clinical state and the extreme impairment of sodium conservation. One may question also whether the renal loss of salt in 'salt-losing nephritis' is due, as is commonly supposed, to a specific impairment of the tubular mechanisms responsible for reabsorbing sodium and chloride from the glomerular filtrate; or whether it is an exaggeration of the tendency to wastage of sodium that can result simply from numerical loss of functional nephrons (Platt, Roscoe, and Smith, 1952).

In the present patient there was a characteristic pattern of excretory function that remained constant throughout the period of investigation: the ratio of plasma to urinary concentrations of urea (urea P/U ratio) varied from 1/3 to 1/4, the sodium P/U remained close to 2/1, and the potassium P/U was equal to or less than that of urea (Fig. 7). An essentially similar pattern has been observed during the osmotic diuresis induced experimentally in dogs and in children by administration of large amounts of urea (Mudge, Foulks, and Gilman, 1949, 1950; Rapoport, West, and Brodsky, 1949). This observation suggests that an osmotic urea diuresis was operating constantly in our patient. It has been found in commonplace renal failure that, as the primary disease advances and glomerular filtration is progressively reduced, the renal tubules reabsorb progressively less of the sodium delivered to them in the glomerular filtrate (Platt, 1950; Nickel, Lowrance, Leifer, and Bradley, 1953). A functionally analogous phenomenon was observed by Mudge and his collaborators in their experiments in dogs: as the plasma level and excretion rate of urea were increased by infusion of urea, progressively more of the filtered sodium remained unabsorbed by the renal tubules. These complementary clinical and experimental observations suggest that the impaired conservation of sodium and

chloride in azotaemic renal failure is due to osmotic diuresis. Platt (1951, 1952) suggested that osmotic diuresis in renal failure results from increased filtration of osmotically active solute by the surviving glomeruli; and it is reasonable to assume that in this condition, as in the normal kidney, increasing loads of filtered solute would increase progressively the rate of sodium excretion. On such a basis it would be possible to account for the development of the syndrome of 'salt-losing nephritis' without invoking a specific defect of tubular function. 'Salt-losing nephritis' may represent merely a variant of destructive renal disease in which the surviving glomeruli are disproportionately hypertrophied and filtering excessively into the attached tubules. Most examples of this syndrome appear to develop in patients with chronic pyelonephritis (Entecknap, 1952), where the absence of a primary glomerulitis may favour glomerular hypertrophy. The much more efficient capacity for sodium conservation observed in other patients with azotaemic renal failure (Platt, 1950; Neubauer, Magee, and Dunsmore, 1954) may reflect the presence in the diseased kidneys of glomeruli that are partly obliterated and thus not filtering excessively. Any further reduction of glomerular filtration in such patients could so reduce the osmotic diuresis that the load of sodium reaching the distal tubule falls within its capacity for sodium reabsorption. These arguments alone will not eliminate the possibility of a specific defect in the tubular reabsorption of sodium in 'salt-losing nephritis'; but the mechanistic concept of varying degrees of 'glomerular-tubular imbalance' would most simply account for the unpredictably variable capacity for salt conservation which is known to occur among azotaemic patients. Moreover, it must be emphasized that the failure of deoxycortone to reduce the urinary output of sodium in 'salt-losing nephritis' is by no means indicative of a specific 'tubular unresponsiveness', as has commonly been supposed. In the first place, azotaemic patients not sustaining large losses of salt have also failed to respond to deoxycortone (Spühler and Zollinger, 1953); and, secondly, a demonstrable response cannot logically be expected when the endogenous production of aldosterone is greatly increased, as it was in our own patient.

The present observations show that a patient with renal salt-wasting, like most other patients with renal failure, responds to the deprivation of salt with a fall in urinary volume and reduction in the output of sodium. The urinary concentration of sodium is reduced (Fig. 7), and there is an apparent increase in the reabsorption of sodium by the tubules (Table IV). Although observations on the present patient could not be continued to prove the point, it seems probable that the output of sodium could fall to reach the level of dietary intake, with establishment of a new external equilibrium in a state of sodium deficiency. Recently published data of Knowles, Levitin, and Bridges (1957) indicate that external balance was achieved in their patient on the sixth and seventh days after reducing the daily intake of sodium from 200 to 71 m-equiv. In many other recorded cases of the syndrome, the clinical history alone suggests that the patient attained external balance in a state of salt deficiency, and even in the presence of oligaemia. Not infrequently, for a period of months before becoming

critically ill, the patient has experienced symptoms of sodium deficiency such as muscular cramps, anorexia, nausea, weakness, and loss of weight, or symptoms of oligaemia such as hypotension and postural giddiness. Unless one is alert to the possibility that some of the symptoms experienced by an uraemic patient are specifically due to a deficiency of sodium, the diagnosis of a salt-losing state may be missed. In such a patient oliguria may represent a 'normal' daily urinary volume of 1·5 to 2 litres (see Fig. 6), and both the high urinary concentration of sodium and a measured 'normal' daily output of sodium may suggest that the patient is in balance with an average dietary intake of salt. It may not be easy to detect clinically a moderate deficiency of sodium; and, in the chronically uraemic patient, if the serum level of sodium is reduced (less than 136 m-equiv. per litre) and the blood-pressure is normal or low, there is much to be said for observing the effect of sodium administration (50 to 200 m-equiv. daily). A beneficial response may uncover a 'compensated' state of salt wasting, and provision of a regular supplement of salt will then reduce the degree of azotaemia, improve well-being, and often prolong life.

If the therapeutic dose of sodium is increased progressively in patients with the salt-wasting syndrome, exceptionally high rates of urinary flow may be produced. Daily outputs of five to seven litres (Milliez, Laroche, and Funck-Brentano, 1954), eight litres (Gjorup, 1954), and even 10 litres (Borst, 1949–50), have been recorded in patients receiving from 60 g. (1,025 m-moles) to 134 g. (2,290 m-moles) of sodium chloride daily. Yet it is the rule for patients with this syndrome to become stabilized with a daily intake of sodium chloride close to 20 g. and a urinary volume that rarely exceeds four litres. We consider these very high volumes to be spurious and unrelated to the severity of the renal lesion; they reflect rather the efficiency of the diseased kidneys in disposing of misguided therapy. One could, indeed, regard the occurrence of gross polyuria as providing support for the hypothesis of exceptionally high filtration rates in the surviving nephrons. Most patients with chronic renal failure would be quite unable to excrete a daily therapeutic load of sodium equivalent to one-half the normal level of total body sodium (the 2,290 m-moles given to the patient of Borst (1949–50)); circulatory overloading and cardiac failure may develop with much smaller doses of salt, and Platt (1950) has described this occurrence in a patient who received no more than 5 g. NaCl for four days.

Gross disorders of potassium metabolism develop occasionally in patients with conventional renal failure (Schoch, 1951), but they are impressively frequent among the recorded cases of 'salt-losing nephritis'. Both hypokalaemia and hyperkalaemia have been described (Murphy, Coffman, Pringle, and Iseri, 1952; Gjorup, 1954; Read, 1956; Levere and Wesson, 1956), and each has sometimes been accompanied by flaccid muscular paralysis. It is obvious, both from the present study and from the observations of Murphy and his collaborators, that these complications reflect the limited capacity of the kidneys to vary the output of potassium. In the hydrated patient a reduction of potassium intake is not followed by an appropriate decrease in urinary potassium. Consequently potassium deficiency and hypokalaemia are particularly likely to

develop when a sodium-deficient patient, who is eating nothing, is treated with replacement infusions containing sodium salts only (Murphy, Coffman, Pringle, and Iseri, 1952; Gjorup, 1954). With developing dehydration and acidosis, more potassium is released from cells to the extracellular fluid than the diseased kidneys are able to excrete; a dangerous degree of hyperkalaemia may then arise, even if the external balance of potassium is negative (Fig. 3).

It is implicit in the foregoing discussion that the patient with 'salt-losing nephritis' differs only in degree from the generality of cases of azotaemic renal failure. He provides a caricature of the problems of renal failure. The various clinical and biochemical complications experienced by our patient may develop, if less readily, in any chronically uraemic patient. The renal lesions in 'salt-losing nephritis' (Enticknap, 1952; Darmady and Stranack, 1955) do not differ distinctively from the findings in chronic renal failure (Oliver, 1939). Even the characteristic salt-wasting can be explained reasonably in terms of the osmotic hypothesis proposed to explain other phenomena of renal failure; and the general impairment of salt conservation in uraemia is universally recognized. It seems to us superfluous to invoke the concept of a specific defect of tubular function to account for the extreme variant of a common clinical state.

Adaptations to the chronic wastage of salt; the hazards attending therapy. In neither of the two observed episodes of salt-depletion in the present patient were the serum levels of sodium and chloride greatly reduced; the lowest serum-sodium level was 128 m-equiv. per litre and, except when the patient was receiving sodium bicarbonate, the lowest serum-chloride level was 100 m-equiv. per litre. This finding is in contrast with certain other reported cases, in which the serum level of sodium has fallen below 120 m-equiv. or even below 110 m-equiv. per litre. In some of these cases the diagnosis has been in doubt, and they might be regarded as instances of so-called 'symptomless hypotonicity' rather than salt-losing renal disease. The two tuberculous patients (Cases 1 and 2) of Joiner and Thorne (1952), and Case 4 of Murphy, Settimi, and Kozokoff (1953), with bacterial endocarditis and heart failure, are suspect in this context. In other patients with very low levels of serum sodium (Murphy, Settimi, and Kozokoff, 1953; Gjorup, 1954; Read, 1956) the daily intake of fluid is not stated; while in still others, such as the patient of Murphy, Coffman, Pringle, and Iseri (1952), it is certain that the patient was receiving either large infusions of *hypotonic* replacement solutions or an enforced huge daily intake of water by mouth. It is consequently not surprising that what appear to be episodes of water intoxication appear in the clinical histories (Murphy, Coffman, Pringle, and Iseri, 1952; Hunter and Muirhead, 1952; Gjorup, 1954; Read, 1956). The patient with renal failure is unable to initiate a water diuresis, and his principal safeguard against over-hydration is the sensitivity of his thirst mechanism. The mental changes that accompany a severe deficiency of sodium are likely to blunt this mechanism, but the patient will rarely intoxicate himself with water. He is, however, in no position to resist the ministrations of his medical attendant; and, as is suggested by the records cited above, the patient meets his greatest risk of water intoxication when treatment is started. There

are two reasons for this; first, the ill-founded notion that the patient able to do so should be compelled to ingest an arbitrary minimum of fluid (as much as six litres of water has been given daily in some recorded cases); second, the frequent use of 'glucose-saline solutions' in which the molarity of sodium chloride is one-half that of normal plasma. The essential requirement of the patient is for sodium and, if parenteral administration is necessary, this can best be met by the use of hypertonic (from molar to one-third molar strength) solutions of sodium chloride and sodium lactate (Black, 1953). The final adjustment of the osmolarity of the body fluids can be left to the patient's voluntary intake of fluid.

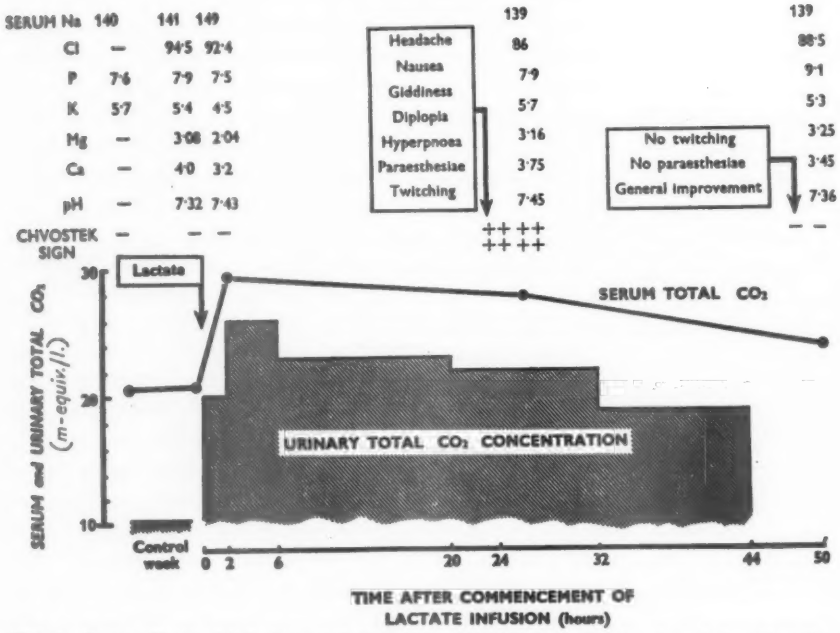


FIG. 8. Some effects of infusing a solution of sodium lactate with the aim of elevating the low level of serum total CO_2.

In the upper part of the diagram biochemical and clinical data are charted (see text); with the exception of serum phosphate, which is recorded as mg. per 100 ml., figures for electrolytes are given as m-equiv. per litre. Below are recorded the changes in the concentration of total CO_2 in serum and urine, to demonstrate the crude parallelism between the two.

There is no physiological mechanism comparable with thirst that will ensure an adequate intake of salt in response to its excessive loss, and we have found only one report of 'salt-craving' in this syndrome (Knowles, Levitin, and Bridges, 1957). It is also difficult in practice to determine the optimum intake of salt for the individual patient. Too much salt may promote the excessive but harmless polyuria that has already been discussed; but polyuria will develop only if the kidneys remain capable of excreting the excess. The greater hazards

arise if salt is retained, when the major problem is the development of hypertension and heart failure. Occasionally it may be extremely difficult to strike a balance between the dose required to repair salt depletion and the slight excess that precipitates cardiac failure; and the patient's clinical state may oscillate precariously between these two extremes (R. I. S. Bayliss, personal communication). The dose appropriate to each patient can be determined only by cautious trial. Nussbaum, Bernhard, and Mattia (1952) suggested that the use of alkaline sodium salts for replacement may be detrimental; but the reasons for this belief do not emerge clearly in their paper. Obvious potential sources of trouble are the production of hypokalaemia (*vide supra*) and of alkalosis, which might be more serious if the patient also had hypocalcaemia. Our own experience of their continued use indicates that the alkaline salts of sodium can be used with sodium chloride to limit the physiologically acidifying effect of the latter salt. Another experience suggests that it may not always be wise to increase the dose of alkalis with the aim of producing a theoretically 'normal' level of serum bicarbonate. When our patient was well and considered replete with sodium, we attempted to correct her apparent acidosis (plasma total CO_2 21 m-moles per litre) with an infusion containing 250 m-moles of sodium lactate in hypertonic solution. The clinical and biochemical changes that followed this procedure are shown in the upper part of Fig. 8. It will be seen that the maximum change in plasma total CO_2 and plasma pH was apparent soon after completing the infusion, but that symptoms of tetany did not develop until 24 hours later. The tetany was accompanied by hyperpnoea, and by neurological symptoms, headache, nausea, giddiness and diplopia, the cause for which is not clear. The delayed development of the clinical symptoms is not explained by change in any of the biochemical variables measured. Most of the administered sodium was retained and, 24 hours after the infusion, it is estimated that the volume of the extracellular fluid had increased by approximately 1·6 litre, but we see no obvious way in which this could have been contributing to the production of the patient's symptoms. Although unable to explain this unpleasant clinical experience, we place it on record as a caution against the possibly adverse effects of excessive alkali.

Adrenal cortical function in 'salt-losing nephritis'. The greatly increased output of aldosterone by the present patient must be regarded as an adrenal cortical response to the chronic loss of sodium. Luetscher and Curtis (1955) have also reported high urinary aldosterone levels in a case of 'salt-losing nephritis', but the level returned to normal when their patient was provided with an adequate supplement of sodium chloride. Hernando, Crabbé, Ross, Reddy, Renold, Nelson, and Thorn (1957) recorded without further comment high values of urinary aldosterone in two patients with 'salt-losing nephritis', whose intake of sodium at the time of assay was described as 'high'. The output in our own patient was still high when her daily intake of sodium exceeded 400 m-equiv. (Table III), suggesting that the production of aldosterone had become independent of the body sodium. A single, greatly increased value for urinary aldosterone in a second patient is recorded in the note to Table III. We are

unaware of any other direct observations on aldosterone production in this syndrome, but it is probably significant that very large adrenal glands have been found at autopsy (Table V); several of the patients there recorded continued to take an adequate supplement of salt up to the time of death. It is possible that adrenocortical hyperplasia may be the structural counterpart of the apparently autonomous production of aldosterone observed in the present patient. The precise stimulus to aldosterone production is unknown, although

TABLE V

The Adrenal Glands in Patients Sustaining Renal Wasting of Salt

Authors	*Total weight (g.)*	*Additional features*
Thorn, Koepf, and Clinton (1944) Case 1	40·5 (16·5, 24)	Golden-yellow cortex; large spherical nodule at one pole of left gland
Case 2	16 (7·5, 8·5)	Considerable lipid in cortex
Sawyer and Solez (1949)	*c.* 40 (21, 21 ?)*	Cortex twice normal thickness, with small hyperplastic nodules or adenomata
Borst (1949–50)	Not recorded	'Normal in structure'
Nussbaum, Bernhard, and Mattia (1952)		Small adrenocortical adenoma
Murphy, Coffman, Pringle, and Iseri (1952)	20	Cortex 3 mm. in thickness. Zona fasciculata wide, making up most of cortex; cells distended with lipid material
Joiner and Thorne (1952) Case 3	40 (20, 20)	†Histologically indistinguishable from normal
Murphy, Settimi, and Kozokoff (1953) Case 3	Not recorded	'Normal except for slight nodular hyperplasia of the cortices'
Ericson and Svanborg (1955) Case 1	24·5	†Diffuse hyperplasia, especially of the fascicular zone; in some places slight nodular hyperplasia of cortex
Case 2	18·5	†Diffuse cortical hyperplasia, especially of reticular zone; cells of fascicular zone rich in lipid
Milne (1956) (unpublished)	29 (15, 14)	†Cortical hyperplasia only, with much lipid storage

* One gland was torn in removal; it was judged to equal the opposite gland in weight.
† Details communicated to the authors by Drs. J. B. Enticknap, M. D. Milne, and A. Svanborg.

It will be noted that the combined adrenal weight was increased in all cases where the measurement was made. Dawson (1956) found the average combined weight of the adrenal glands to be 11·8 g. in 90 subjects with normal blood-pressure, 15·3 g. in 90 subjects with essential hypertension, and 15·7 g. in 44 patients with renal hypertension. In the above patients with 'salt-losing nephritis' there was no common pattern of histological change, and no report suggests predominant hyperplasia of the zona glomerulosa. The frequent mention of 'nodular' or 'adenomatous' change is of interest; it may be related to the apparent functional autonomy shown in the present patient (see text).

sodium deficiency, decreased blood volume, and perhaps also elevation of the serum level of potassium, will increase its rate of secretion (*Lancet*, 1957). All patients with 'salt-losing nephritis' have suffered depletion of sodium and of blood volume, often for long periods of time, and in many the serum level of potassium has also been high. Conditions are thus optimal for the secretion of aldosterone, and the observations made on the present patient suggest that long-continued stimulation may ultimately lead to autonomy of hormonal production. There is a little additional evidence to support this belief. Increase of body sodium, with expansion of the extracellular fluid volume, was less effective in reducing the increased secretion of aldosterone in cardiac failure and hepatic cirrhosis than in inhibiting normal secretion (Gordon, 1955; Duncan, Liddle, and Bartter, 1956). More direct evidence for autonomous secretion was provided by a patient with chronic generalized oedema, who had been treated for years

by a restricted intake of sodium and the vigorous use of diuretics (Thorn, Ross, Crabbé, and van't Hoff, 1957). It was considered that hyperaldosteronism in this patient resulted from chronic deprivation of sodium, but the output of aldosterone was little affected by increasing the intake of sodium. An aldosterone-secreting adenoma was removed with one adrenal gland, but subsequently the remaining, and structurally normal, adrenal gland resumed the excessive formation of aldosterone. There is an obvious analogy between the functional state in this patient and that found in patients with renal salt-wasting; and it is of interest that 'adenomatosis' of the adrenal cortex may develop in the latter syndrome (Table V). Florid renal salt-wasting is uncommon, but in cases recognized subsequently much might be learned from a detailed study of the factors influencing aldosterone secretion.

We are grateful to Dr. F. Wemyss Smith for referring the patient to us, and to Drs. A. H. Gowenlock, J. F. Tait, and S. A. Simpson for the assays of aldosterone. During the course of this work Dr. R. F. Mahler was in receipt of a personal full-time grant from the Medical Research Council; his present address is the Department of Therapeutics, Queen's College, Dundee, Scotland.

Summary

In a patient with renal failure and the clinical syndrome of 'salt-losing nephritis', metabolic observations have been made during the development and subsequent correction of a severe deficiency of sodium. In spite of a grossly impaired renal capacity to conserve sodium, the loss of sodium was limited by a progressive fall in its urinary output towards the level of dietary intake.

The acutely developing deficiency of sodium initiated a catabolic response that contributed to the production of increased serum levels of urea and potassium. The renal capacity to vary the output of potassium was strictly limited, and the serum level of potassium was determined primarily by shifts of this ion between cells and extracellular fluid with changes of acid-base balance.

The urinary output of aldosterone was greatly increased long after the deficiency of sodium had been corrected. It is suggested that the adrenal secretion of aldosterone may become autonomous after a prolonged period of stimulation. Attention is drawn to the finding of gross adrenocortical hyperplasia in the recorded autopsies in 'salt-losing nephritis'.

It is suggested that the pattern of renal function in azotaemic renal failure is compatible with a constantly operating osmotic diuresis, which results from the entry of an increased load of solute into the surviving nephrons. Reduced tubular reabsorption of sodium and chloride would follow as a physiological consequence of osmotic diuresis; and, in the 'salt-wasting' syndrome, the greater renal loss of salt may result simply from a quantitatively greater osmotic loading and a consequently more intense osmotic diuresis. After the therapeutic provision of a supplement of sodium salts, a greater load of sodium is filtered into each nephron; the osmotic effect of this additional sodium increases

the tubular diuresis and reduces the reabsorption of urea and water. The result is an increase in urinary volume and a fall in the body content of urea.

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TREATMENT OF TUBERCULOUS MENINGITIS[1]

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One of the controversial problems in medicine in recent years has been the treatment of tuberculous meningitis, in particular as to whether or not the intrathecal administration of streptomycin is required. Attention has again been focused on this topic by the findings of a Scottish Joint Committee (1957). It is apparent from subsequent correspondence that there is still considerable opinion against the omission or reduction of intrathecal treatment, and this view corresponds with the bulk of the earlier literature (for example, Robertson and Gairdner, 1952; Lincoln and Sifontes, 1953; Torres-Gost, 1953; Robinson and Ro, 1954; Smith, Vollum, Taylor, and Taylor, 1956). Nevertheless, in support of the contention that intrathecal medication may be unnecessary, a further analysis of results of treatment of tuberculous meningitis is presented here, the analysis taking into consideration not only the question of survival, but also the sequelae of the disease. The results are those obtained in the Northern Ireland Fever Hospital, Belfast, between August 1947 (when streptomycin became available at the hospital) and December 1955. In these years 207 patients with tuberculous meningitis were treated.

In reviewing the case notes it was found that the patients could be divided, according to the treatment they received, into three groups:

Group I: those who were given streptomycin by intramuscular and intrathecal injection;

Group II: those who were given dihydrostreptomycin by intramuscular and intrathecal injection;

Group III: those who were given streptomycin by intramuscular but not by intrathecal injection; they also usually received *p*-aminosalicylic acid (PAS) or isoniazid, or both.

The determining factor as to which type of treatment a patient received was simply the date on which the patient came under hospital care. Thus all patients admitted between August 1947 and May 1952 (excepting 13 months from August 1950 to September 1951) received intramuscular and intrathecal streptomycin. The dosages given at first were: intramuscularly, 10 mg. per kg. of body weight per day in four-hourly or six-hourly injections; intrathecally, 50 to 100 mg., according to the patient's weight. Later the intramuscular dosage was reduced to 5 mg. per kg. per day, in two 12-hourly injections, continued, in those cases

[1] Received September 1, 1958.

in which the patient survived and no serious toxic effects occurred, for approximately six months. Other minor variations as regards dosage, frequency, and duration of treatment were made from time to time. A small number of patients received other drugs in addition to the above: eight patients were given heparin (1948), 26 streptokinase (1949 to 1951) and four intrathecal tuberculin (P.P.D.) (1950). During a 13-month period in 1950–51 dihydrostreptomycin was used by intramuscular and intrathecal injection. After the introduction in 1952 of isoniazid, and in spite of numerous pessimistic reports (for example, Robertson

TABLE I

Comparison of Treatment Groups in Respect of Severity of Illness

Severity of illness	*Treatment group*			
	I	*II*	*III*	*Total*
A	8 (6·7)	2 (6·1)	23 (42·6)	33 (15·9)
B	97 (80·8)	26 (78·8)	21 (38·9)	144 (69·6)
C	15 (12·5)	5 (15·1)	10 (18·5)	30 (14·5)
Total	120 (100)	33 (100)	54 (100)	207 (100)

χ^2 43·5547
Degrees of freedom: 4
Probability: $P < 0{\cdot}001$

Note. In all tables the numbers in parentheses indicate percentages.
In certain tables, it has been necessary to group data to facilitate the χ^2 test.
The conventional level of $P > 0{\cdot}05$ is accepted throughout this paper.

and Gairdner, 1952; Kendig, Trevathan, and Ownby, 1954), intramuscular streptomycin was given combined with isoniazid and PAS, without any intrathecal treatment. Later, intramuscular streptomycin and isoniazid alone were used, and this scheme was continued up to December 1955. Since December 1955 there has been no significant alteration in the methods of treatment, or in the results as described below; the figures are too small to submit to statistical analysis.

Although it has been possible, for purposes of comparison, to divide the cases of this series into three groups, an obvious criticism lies in the fact that the groups were not 'controlled', for example, by giving alternate patients intramuscular treatment and combined intramuscular and intrathecal treatment respectively. The grouping has, in fact, been largely chronological, the treatment accorded to any patient being that which was considered the best at the time when the diagnosis was made. To overcome such objections the homogeneity of the treatment groups has been tested in retrospect, such possible factors as might have affected survival rate, or sequelae among survivors, being selected and considered individually. The possible variables examined were as follows:

(1) *Severity of illness.* All cases were designated A (mild), B (moderate), or C (advanced), at the time when treatment was commenced, this classification being the same as that used by the Medical Research Council (1948) in their original streptomycin trials. A comparison has been made between the severity of the cases in the three treatment groups. From the results of a χ^2 test (Table I)

it is apparent that a significant difference existed between the groups, the major contribution to this difference being due to a preponderance of milder cases in Group III.

(2) *Initial sugar levels in the cerebrospinal fluid.* It is usually agreed that the severity of tuberculous meningitis is reflected accurately by a fall in the cerebrospinal-fluid sugar level. With a preponderance of milder cases among the patients in Group III, a corresponding difference might be expected in the cerebrospinal-fluid sugar levels found in the three groups. This proved to be the case: the mean values were lower in Groups I and II than in Group III, and these differences were shown to be significant on an analysis of variance; differences in distributions of the sugar levels were also significant as assessed by the χ^2 test. To conserve space, the actual figures are not given, but the tests employed and the results are tabulated together (Table III).

TABLE II

Incidence of Meningeal and 'Combined' Cases

	Treatment group			
Nature of disease	*I*	*II*	*III*	*Total*
Meningitis alone	113 (94·2)	28 (84·8)	44 (81·5)	185 (89·4)
Meningitis and miliary tuberculosis	7 (5·8)	5 (15·2)	10 (18·5)	22 (10·6)
Total	120 (100)	33 (100)	54 (100)	207 (100)

(3) *Initial protein levels in the cerebrospinal fluid* were estimated in the same samples as the sugar estimations, and the figures were similarly treated. No significant differences were obtained between the three treatment groups, and this may be due to the fact that the protein level reflects the severity of tuberculous meningitis less accurately than the sugar level.

(4) *Duration of illness before treatment commenced.* Tuberculous meningitis untreated is progressive, the severity increasing the longer the patient is left without treatment. The number of days that each patient had been ill before treatment commenced was therefore determined as accurately as possible, because it was felt that, if this factor differed materially between the three treatment groups, it would be a further index of differences in severity. From the results of an analysis of variance and the χ^2 test it was shown that no such differences existed.

(5) *Age and* (6) *sex of the patient.* These two factors were considered, although neither was regarded as being necessarily related to severity, or to ultimate prognosis. No significant differences were detected from the figures submitted to the χ^2 test.

(7) *Presence of tuberculous lesions other than meningeal.* The coexistence of pulmonary or osseous tuberculosis with tuberculous meningitis did not seem of importance as regards survival from the latter disease. It has been suggested, however, that the presence of acute miliary tuberculosis in conjunction with

tuberculous meningitis gives a worse prognosis than meningitis occurring alone. Although this view is not necessarily supported (and has been denied by certain workers), the figures pertaining to meningitis and to 'combined' cases have been compared between the three treatment groups. The numbers were small, and a value of χ^2 could be obtained only in comparing Group I with Group III and Group II with Group III. Groups I and II were compared by determining an exact probability. A greater incidence of 'combined' meningeal and miliary lesions was observed in Group III (Table II) as compared with Group I, although not with Group II, and this increased incidence was found to be significant.

TABLE III

Homogeneity of the Three Treatment Groups

Tests employed and values of P

Variable	*Test*	*Probability*
Severity of illness	χ^2 test	$P < 0{\cdot}001$
Duration before treatment	Analysis of variance	$P > 0{\cdot}2$
	χ^2 test	$0{\cdot}5 > P > 0{\cdot}3$
Cerebrospinal fluid:		
initial sugar level	Analysis of variance	$P < 0{\cdot}001$
	χ^2 test	$0{\cdot}02 > P > 0{\cdot}01$
initial protein level	Analysis of variance	$P > 0{\cdot}2$
	χ^2 test	$0{\cdot}7 > P > 0{\cdot}5$
Sex of patient	χ^2 test	$0{\cdot}9 > P > 0{\cdot}8$
Age of patient	Analysis of variance	$P > 0{\cdot}2$
	χ^2 test	$0{\cdot}3 > P > 0{\cdot}2$
Meningitis and miliary tuberculosis	Exact probability (Groups I and II)	P (single tail) 0·9774
	χ^2 test (Groups II and III)	$0{\cdot}95 > P > 0{\cdot}90$
	χ^2 test (Groups I and III)	$0{\cdot}02 > P > 0{\cdot}01$
District (urban or rural)	χ^2 test	$0{\cdot}7 > P > 0{\cdot}5$
Family history of tuberculosis	χ^2 test	$0{\cdot}7 > P > 0{\cdot}5$
Social class of patient	χ^2 test	$0{\cdot}3 > P > 0{\cdot}2$

This was a surprising result because, if the severity in cases of combined meningeal and miliary disease is greater than in meningitis occurring alone, Group III would be expected to contain more severe cases than the other two groups, whereas the opposite has been shown to be true. Furthermore, the higher incidence of miliary lesions in patients of Group III may be explained by the fact that they were all under treatment between the later months of 1952 and December 1955. During this period radiological facilities were available at the hospital, and more cases with miliary involvement were detected than in the years 1947 to 1950, when most of the patients of Group I were investigated and treated. It is probable that the incidence of miliary tuberculosis was the same during both these periods, and that the difference which appears in comparison of the figures for both periods is not valid.

(8) *The district* (*urban or rural*) in which the patient lived; (9) *the presence of tuberculosis*, or a history of previous tuberculous infection, in the patient's family; and (10) *the social class* (*graded I–V*) to which the patient belonged, determined by the patient's occupation or, in the case of a child, by the parent's

occupation. These three factors were considered in comparing the three treatment groups, a χ^2 test being applied to each set of data. No significant differences were found.

TABLE IV

Comparison of Treatment Groups in Respect of Survival or Death

	Treatment Group						
	I		*II*		*III*		
Outcome	*Observed*	*Expected*	*Observed*	*Expected*	*Observed*	*Expected*	*Total*
Survival	46 (38·3)	47·3752 (39·5)	3 (9·1)	14·4375 (43·7)	45 (83·3)	32·1874 (59·6)	94 (45·4)
Death	74 (61·7)	72·6248 (60·5)	30 (90·9)	18·5625 (56·3)	9 (16·7)	21·8126 (40·4)	113 (54·6)
Total	120 (100)	120 (100)	33 (100)	33 (100)	54 (100)	54 (100)	207 (100)
	χ^2S 0·0399		χ^2S 9·0609		χ^2S 5·1003		
	χ^2D 0·0260		χ^2D 7·0473		χ^2D 7·5261		

χ^2 28·8005
Degrees of freedom: 2
Probability: $P < 0·001$

TABLE IV(*a*)

Comparison of Treatment Groups I and II

	Treatment Group				
	I		*II*		
Outcome	*Observed*	*Expected*	*Observed*	*Expected*	*Total*
Survival	46 (38·3)	38·1130 (31·8)	3 (9·1)	10·8870 (33·0)	49 (32·0)
Death	74 (61·7)	81·8870 (68·2)	30 (90·9)	22·1130 (67·0)	104 (68·0)
Total	120 (100)	120 (100)	33 (100)	33 (100)	153 (100)

χ^2 10·9184
Degrees of freedom: 1
Probability: $P < 0·001$

TABLE IV(*b*)

Comparison of Treatment Groups II and III

	Treatment Group				
	II		*III*		
Outcome	*Observed*	*Expected*	*Observed*	*Expected*	*Total*
Survival	3 (9·1)	12·9295 (39·2)	45 (83·3)	35·0705 (64·9)	48 (55·2)
Death	30 (90·9)	20·0705 (60·8)	9 (16·7)	18·9295 (35·1)	39 (44·8)
Total	33 (100)	33 (100)	54 (100)	54 (100)	87 (100)

χ^2 20 5578
Degrees of freedom: 1
Probability: $P < 0·001$

Table III. This composite table indicates the value of P for each variable described above. It will be seen that the three treatment groups are similar in all respects except (1) in the severity of some of their cases; (2) in the initial diagnostic sugar levels in the cerebrospinal fluid; and (3) in the incidence of

combined miliary and meningeal tuberculosis. The last-named factor is held to be invalid for the reasons stated, so that, in finally assessing the survival rates, and the morbidity among the survivors, of the three treatment groups, only (1) and (2) need be taken into account.

Survival. The numbers of survivors in the three treatment groups are shown in Table IV. The figures have been submitted to a χ^2 test embracing a method of standardization which allows for the possible effects of the two factors which were shown to vary between the three groups. Furthermore, Groups I and II, II and III, and I and III have been paired for comparison (Table IV (*a*), (*b*), and (*c*)). The conclusion which must be drawn from these figures is that Group

TABLE IV(*c*)

Comparison of Treatment Groups I and III

	Treatment Group				
	I		*III*		
Outcome	*Observed*	*Expected*	*Observed*	*Expected*	*Total*
Survival	46 (38·3)	54·8273 (45·7)	45 (83·3)	36·1727 (67·0)	91 (52·3)
Death	74 (61·7)	65·1727 (54·3)	9 (16·7)	17·8273 (33·0)	83 (47·7)
Total	120 (100)	120 (100)	54 (100)	54 (100)	174 (100)

χ^2 9·1418
Degrees of freedom 1
Probability $0{\cdot}01 > P > 0{\cdot}001$

III (intramuscular streptomycin combined with oral isoniazid or PAS or both, but without any intrathecal streptomycin) gave a significantly higher survival rate than Group I (combined intramuscular and intrathecal streptomycin); the results in each of these groups were superior to those obtained in Group II (dihydrostreptomycin). Since other factors have been eliminated, the cause of these differences must ultimately lie in differences in the treatment. In other words, streptomycin by intramuscular injection combined with oral isoniazid or PAS or both, but without any form of intrathecal medication, is best in the treatment of tuberculous meningitis. How much credit for the improvement in survival rate is due to isoniazid or PAS is difficult to assess from the data presented here; the salient fact remains, however, that, provided one is prepared to use the other drugs (and the use of more than one drug is now an accepted principle of any form of antituberculous treatment), no intrathecal streptomycin is required. The discontinuance of intrathecal streptomycin therapy is further to be desired on account of the recognized untoward effects which it sometimes induces, such as repeated convulsions, abrupt pyrexia, and generalized constitutional disturbances, with lethargy, vomiting, and cardiac and respiratory irregularity. There may also be an acute meningeal reaction, with increase in the protein level and cell content of the cerebrospinal fluid, possibly due to the liberation of tuberculin. To these clinical objections may be added the humane consideration of what it means to any patient, child or

adult, if daily intrathecal injections, sometimes repeated for several weeks, can be avoided altogether.

Sequelae in survivors. Apart from survival itself, and in many respects of equal importance with survival, is the problem of the sequelae of tuberculous meningitis. Of the 207 patients treated, 94 survived; although many of these were treated several years ago, contact has been maintained since that time, and it was possible to invite the majority to reattend hospital for examination and assessment. The follow-up examination was conducted on the following lines: interrogation, general physical examination, special examination of the eyes and ears, radiological examination of the chest and skull, electroencephalography in a small number of cases in whom it seemed to be indicated, and assessment of intellectual function and personality. The prime interest lay in deciding whether or not any sequelae existed and, if so, in assessing their severity. It is not proposed to enter into a detailed account of the sequelae, but a list follows of those untoward effects which have been observed. They are given in order, not of frequency, but of their relative importance to the survivor.

1. *Mental changes.* Three children are now undoubtedly mentally defective; one has already required institutional care, and it seems likely that this will ultimately apply to the other two. It is interesting that all three were very young children at the onset of their illnesses (six months, 14 months, and 16 months respectively). Four other children were 'backward' rather than obviously defective, but it is probable that one of these four was always subnormal, being slow in learning to walk and to talk before his illness at the age of three and a half years.

2. *Visual disturbances.* One child was almost completely blind, with bilateral optic atrophy, coarse nystagmoid movement, and moderately dilated immobile pupils. A young woman, although not complaining, was discovered to have a quadrantic hemianopia. A third patient suffered from an attack of choroiditis, six years after his meningitis, presumably allergic in origin and more correctly attributable to generalized tuberculosis than to specific meningeal involvement. A fourth patient complained of recurrent blurring of vision, and, although no cause was found on full examination, she was convinced that this symptom had troubled her only since her illness.

3. *Auditory disturbances.* An immediate difficulty arose in determining whether deafness detected in any of the survivors was, in fact, related to the meningitis, or whether it could have preceded the illness. Another factor is that streptomycin, although more toxic to vestibular function, has some effect on both parts of the eighth nerve. A common finding on routine examination was the presence of meatal wax or débris, or a perforated tympanic membrane, evidence of the previous existence of infective middle ear disease. Allowing for these possible errors, it was finally determined that nine patients in all suffered from some degree of deafness as a result of meningitis.

4. *Vestibular disturbances* were in most cases probably the result of treatment with streptomycin rather than of the meningitis. Vestibular disturbances were

manifested by 18 survivors, usually as ataxia with unsteadiness of gait, especially after dark. It was not possible to demonstrate incoordination in the limbs in these cases on formal testing. Nystagmus was demonstrated in only two cases. There was no complaint of tinnitus. Of the 18 survivors involved, all were treated before December 1953, and two-thirds of them before June 1950. They have all, therefore, experienced their difficulties for a considerable length of time, and it is noteworthy that 10 are improving, while two have no evidence of trouble now, although they had well-marked symptoms on discharge from hospital. These findings support the view that the toxic effects of streptomycin on vestibular function are not irreversible, and that some degree of recovery is possible.

5. *Other central nervous changes.* This group embraces 11 survivors who showed some neurological sequelae other than visual, auditory, or vestibular, as described above. Two patients have had epileptiform seizures since their recovery, without previous history of convulsions, in one case confirmed by electroencephalographic changes. Five patients, all children, showed some degree of muscle weakness in one or more limbs; for example, one boy had the residual weakness of a complete right-sided hemiplegia (he showed further evidence of left-sided cerebral damage in the form of 'word blindness' due to interference in the region of the left angular gyrus). Strabismus of varying severity was encountered in four survivors. One survivor had numerous neurological sequelae, including weakness of the left arm and leg, impaired sensation in the left arm and hand, an unsteady gait, coarse nystagmus, and a partial hemianopia.

6. *Personality changes.* Twenty-eight survivors were considered to show some degree of personality change, ranging from violent outbursts of uncontrolled temper (fortunately in one girl only) to minor aberrations, such as increased irritability or occasional emotional lability which had not been apparent before their illness.

7. *Other changes* were of a minor nature, although a source of annoyance or worry to the patient. They included headaches, skin reactions, loss of a sense of general well-being, lassitude, and increased fatigability; they involved seven patients, and owing to their vague nature it was doubtful whether they could be accurately ascribed to the preceding meningitis.

It has been shown above that there was a larger number of survivors among those patients who were given intramuscular streptomycin with isoniazid or PAS or both (Group III) than among those who received streptomycin or dihydrostreptomycin by intramuscular and intrathecal injection (Groups I and II respectively). Some of the survivors are entirely free of any residual manifestation of their illness, and may be regarded as completely cured; others, unfortunately, have been left with some recognizable defect. The figures relating to the survivors have been submitted to statistical analysis, to determine whether there has been any difference in the results of the various treatments in respect of the sequelae of the disease. Only Groups I and III are analysed; Group II contributed only three survivors, of whom two showed no defect,

and the numbers are therefore too small to be of value in comparison. In dealing earlier with the question of survival rates, it was pointed out that there were differences between the treatment groups in respect of the severity of the cases involved, and also in the initial sugar levels in the cerebrospinal fluid on admission (which might also indicate differences in severity). These factors have therefore been taken into account again in comparing the incidence of residual defects. Table V presents the result of a χ^2 test, in the calculation of which a

TABLE V

Comparison of Treatment Groups in respect of the Incidence of Sequelae

	Treatment Group				
	I		*III*		
Survivors	*Observed*	*Expected*	*Observed*	*Expected*	*Total*
With defect	32 (69·6)	27·2 (59·1)	18 (40)	22·8 (50·7)	50 (54·9)
Without defect	14 (30·4)	18·8 (40·9)	27 (60)	22·2 (49·3)	41 (45·1)
Total	46 (100)	46 (100)	45 (100)	45 (100)	91 (100)
	χ^2+D 0·8485		χ^2+D 1·0133		
	χ^2−D 1·2272		χ^2−D 1·0396		

χ^2 4·1286
Degrees of freedom: 1
Probability: $0{\cdot}05 > P > 0{\cdot}02$

method of standardization was included to allow for the two variables mentioned. In the original calculations it was found that in Group III there were consistently fewer survivors with recognizable defect than the calculated 'expected' number; the reverse was true of survivors without defect. In Group I the 'observed' figure was greater than the 'expected' in the case of survivors with defect, and smaller for survivors without defect. From the figures presented in Table V it is apparent that the survivors of Group III have fewer residual defects than those of Group I, and that this difference is great enough to be significant. The above details refer to all sequelae, irrespective of their severity or importance to the patient. There is no evidence that there were more serious defects in one or the other group, with the possible exception of the mental sequelae; it was noted that the three young children who are now mentally defective (as distinct from being merely retarded) all belonged to Group III. Does this mean that the treatment given to patients in Group III may be followed by a greater number of severe mental disturbances? The suggestion is advanced that such is not the case, but that if these three children had been treated in earlier years, in the same way as patients belonging to Group I, they would probably not have survived their acute illness, or, had they survived, would still have been mentally defective. It seems reasonable to suppose that the higher survival rate in Group III is associated with an increase in the number of severe residual defects simply because patients severely affected initially, and therefore likely to have severe defects, are also more likely to survive if treated by the methods used in Group III. Such results may

well be observed in the future, although they have not as yet come to light except in the present instance.

The conclusion must therefore be that, as regards survival from tuberculous meningitis and residual defects following the disease, the intrathecal administration of streptomycin is not essential, and the best treatment consists of intramuscular streptomycin combined with oral isoniazid or PAS, or both.

I am indebted to Dr. F. F. Kane, Medical Superintendent, Northern Ireland Fever Hospital, for the suggestion that the present study be undertaken, and for kind permission to use his cases.

Summary

Between August 1947 and December 1955 207 patients were treated for tuberculous meningitis at the Northern Fever Hospital; 94 survived, and 113 died. The majority of the survivors have been re-examined recently, and details are given of the sequelae of tuberculous meningitis which have been encountered.

It has been possible for the sake of comparison to divide the patients into three groups according to the treatment they received:

Group I: intramuscular and intrathecal streptomycin.
Group II: intramuscular and intrathecal dihydrostreptomycin.
Group III: intramuscular streptomycin with isoniazid or *p*-aminosalicylic acid, or both, without any form of intrathecal treatment.

The figures pertaining to survival from tuberculous meningitis, and to the presence or absence of sequelae, have been submitted to statistical analysis; the homogeneity of the treatment groups was tested by considering various factors which could have affected the results, allowance being made in the final calculations for two variables which were found to be significant. In this series it has been shown that, as regards both survival and residual defect, the best treatment has been the intramuscular administration of streptomycin combined with oral isoniazid or *p*-aminosalicylic acid, or both, and that intrathecal streptomycin is not essential.

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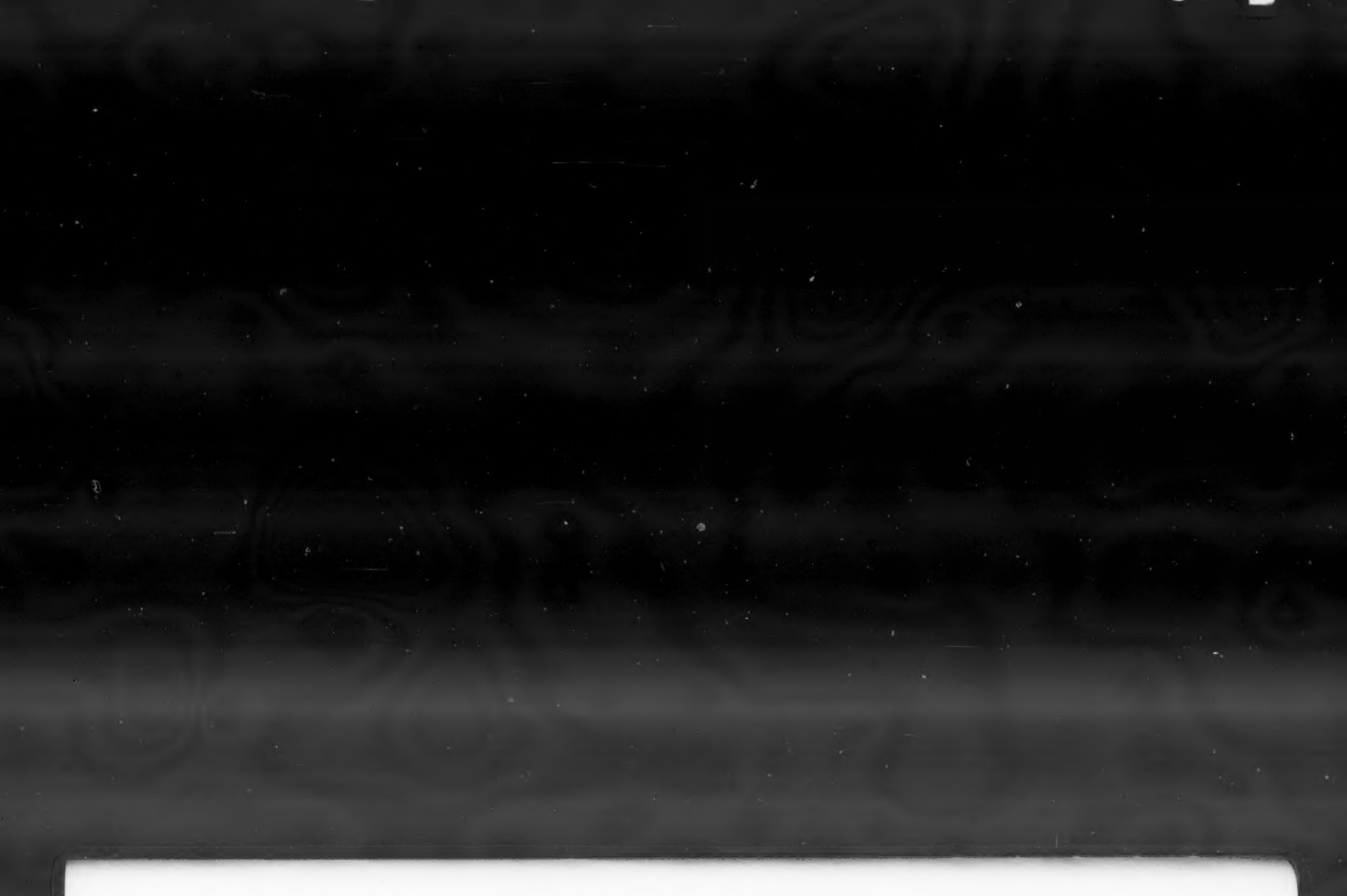

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